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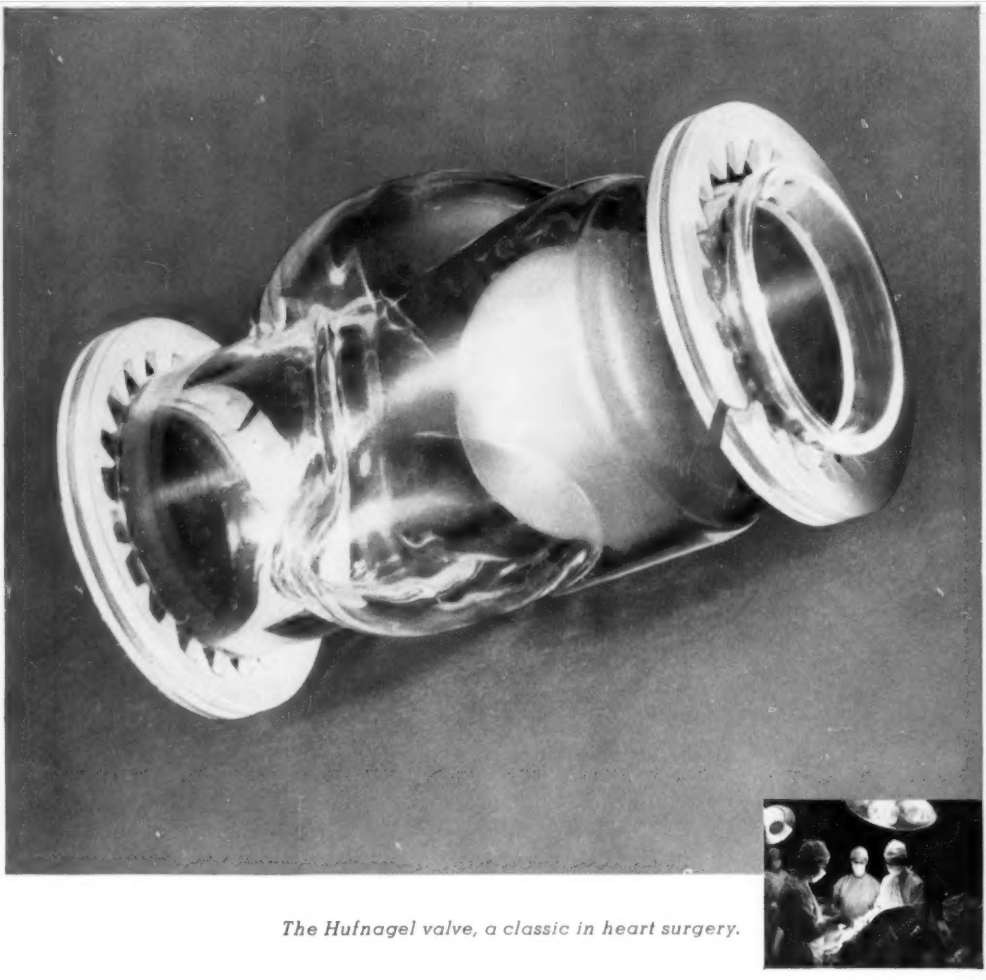

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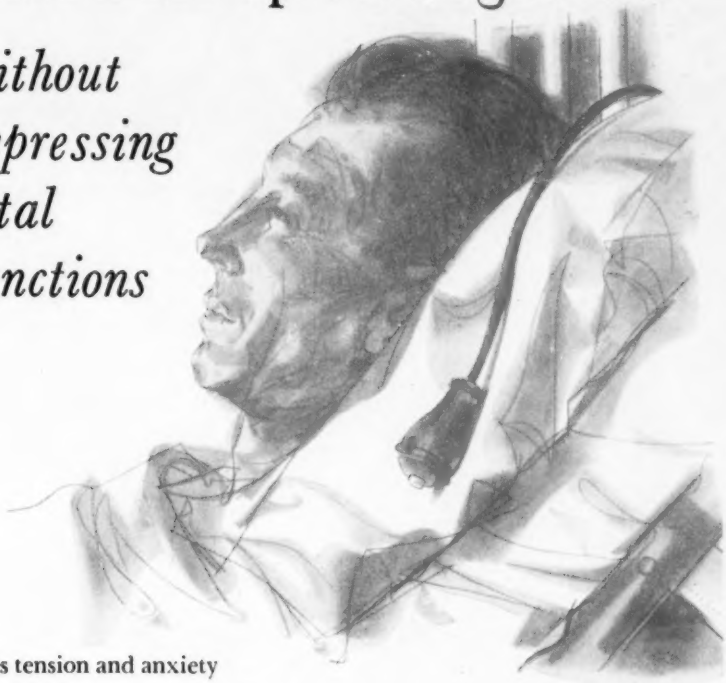

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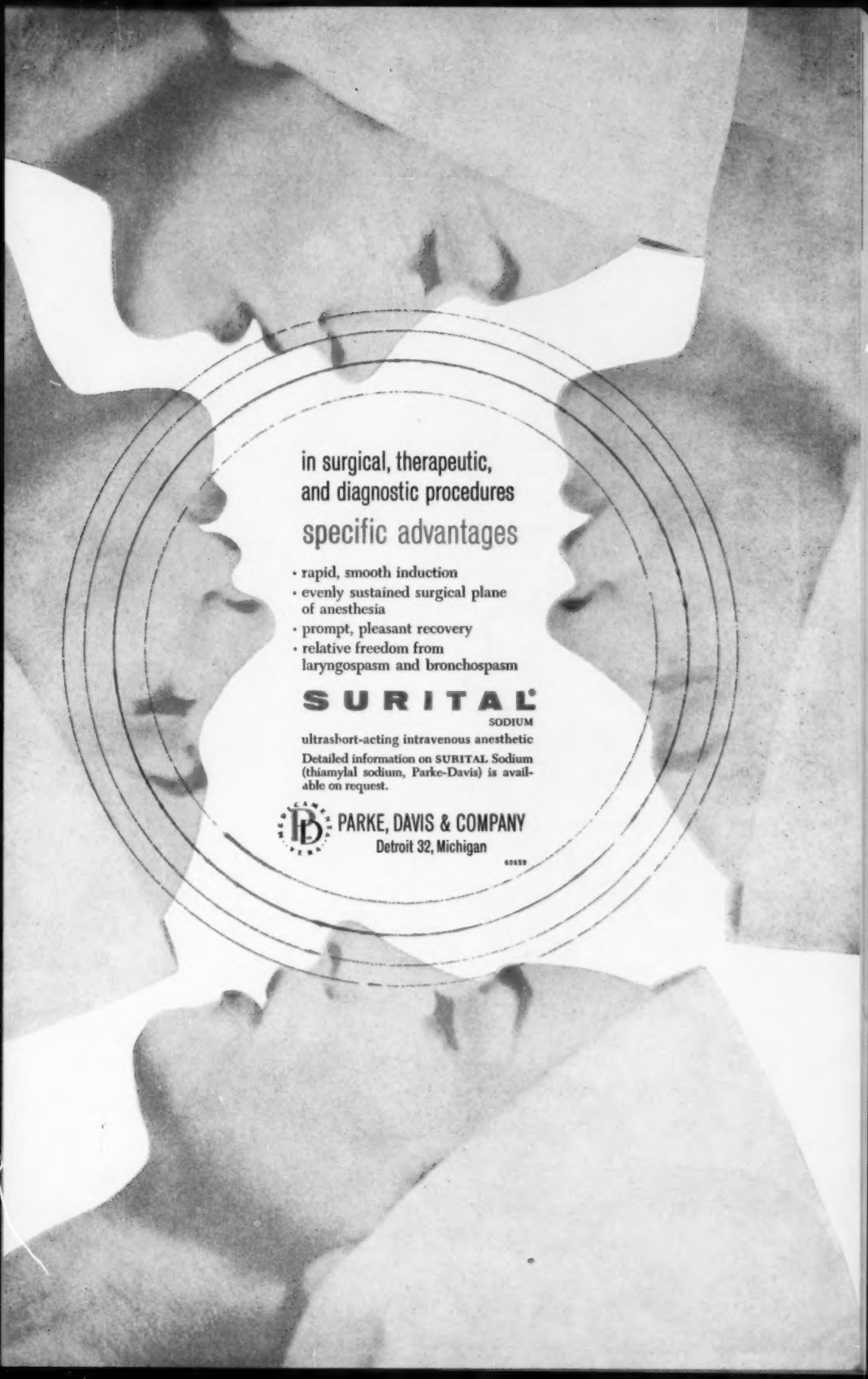
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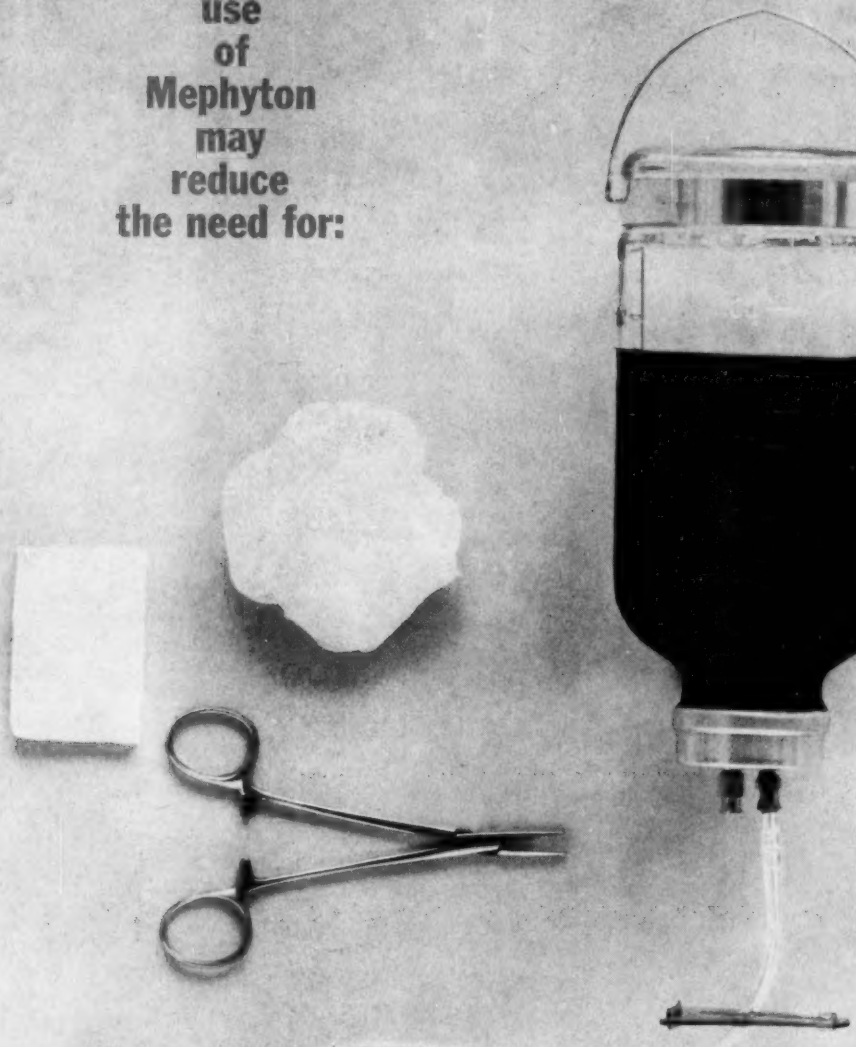

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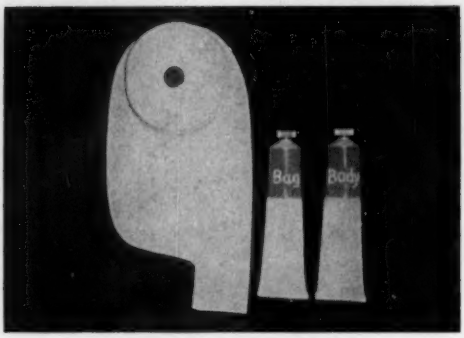

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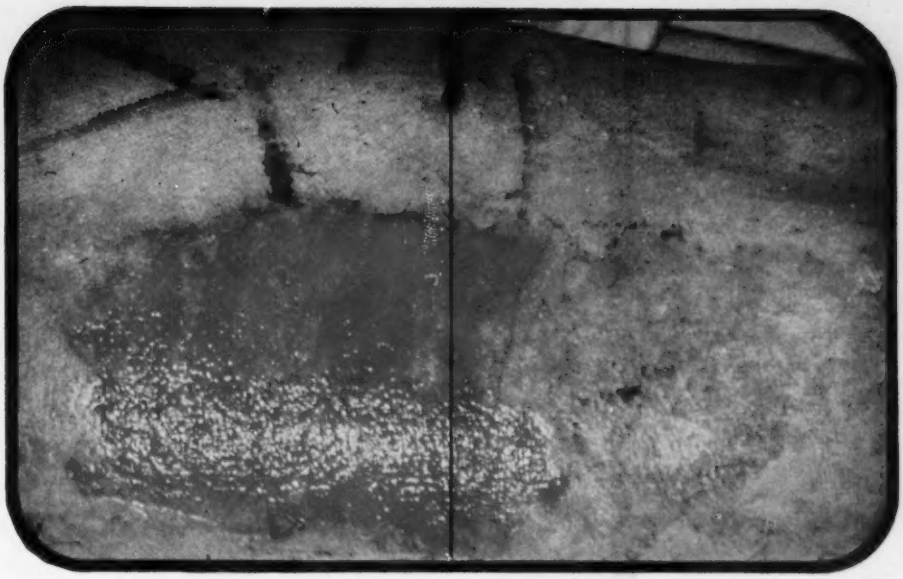

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The Surgical Conscience

W. A. ALTEMEIER, M.D., Cincinnati

My first duty and pleasure is to express to you my deep appreciation for the honor of serving as your president during the past year. I would also like to indicate my gratification for the opportunity of addressing this audience in the City of Montreal, where I have the good fortune to count many personal friends and respected colleagues.

To one who had the privilege of training under Dr. Roy D. McClure, one of the principal founders and first president of this organization, it has been a particular pleasure to watch the development of this young, active, and vigorous society, clearly dedicated to the advancement of the art and science of surgery and unhampered by political factions.

One of the principal advantages of an occasion such as this is the opportunity it affords for the mutual exchange of thought and experience in relation to our special fields of surgical practice in which we are engaged.

In writing an editorial last year on the problem of postoperative wound infection and its significance, I recommended that the "rebirth of the *surgical conscience* and everything that the term implies should be fostered, with instruction of present medical students and interns, and reeducation of the past generation of surgeons to demonstrate the importance of those factors which make up that intangible and valuable asset of a well-trained and capable surgeon." In reflecting further upon this recommendation, many questions have occurred to me: What is the surgical consience? How was it developed? What is its relationship to the lay conscience? Does the surgical conscience differ from the medical? What is its relation to patient care, education, research? How have war, politics, religion, government, and economic conditions influenced it? Is there any evidence that it has deteriorated in recent times, and what have been the results?

In searching the archives of recorded medical history I have been unable to find any dissertation on the development of the surgical conscience, or even a clear definition of it. I will, therefore, permit myself the license of exploring this subject which has had such a marked effect on the surgeon's work and life.

According to "Webster's New International Dictionary," the conscience is defined as follows: "1. Sense or consciousness of the moral goodness or blameworthiness of one's own conduct, intentions, or character, together with a feeling of obligation to do or be that which is recognized as good—often with special reference to feelings of guilt or remorse for ill-doing. Hence a faculty, power, or principle conceived to decide as

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Presidential Address read at the 16th Annual Meeting of the Central Surgical Association, Montreal, Feb. 20, 1959.

From the Department of Surgery of the University of Cincinnati College of Medicine and the Cincinnati General Hospital.

to the moral quality of one's own thoughts or acts, enjoining what is good; as, the still small voice of conscience. 2. Inmost thought or sense; consciousness. 3. Conformity to the dictates of conscience, right or equity. 4. Regard for ordinary fairness or justice, scruple; compunction."

Strictly speaking then, let us assume that the definition of the surgical conscience would be the same as above when applied to the practice of surgery, the training of surgeons, and surgical research.

It is well known that the conscience can be conditioned by education and experience throughout infancy, childhood, and early adulthood. The development of a strong sense of right and wrong, a willingness to help others, a feeling of compassion for the unfortunate, self-discipline, and a strong faith in the sanctity of God and man are fundamental values acquired through education in the home, school, and church. A very significant example is the effect of the "golden rule."

Higher education further develops and modifies the conscience. After first learning to distinguish between two factors as correct and incorrect, one must learn that both may be correct or incorrect under the effect of variables or different circumstances. Then may come the realization that various factors can exist in equilibrium, and that a chain of favorable or unfavorable reactions may result from a disturbance of this equilibrium. More difficult to acquire is the faculty of judgment. This is a product of higher learning and considerable experience resulting in the ability to think independently, to assess the relative value of numerous factors operating in a given circumstance, and to arrive at the best decision or answer. Lack of available facts compounds the difficulty and brings into play wisdom and luck. Thus, judgment becomes a complex exercise in relative values and priorities, and the man whose profession requires it is more exposed to the dictates and pangs of his conscience.

It would seem obvious, therefore, that the surgeon's conscience would depend not only upon his individual moral fiber and religious concepts, but also upon his heritage of philosophical doctrines transmitted to him from the past, his scientific and factual knowledge, and his judgment.

When a young physician begins his surgical training, he is entering one of the most noble professions. Dedicated to the welfare of his patients, he earns the privilege of studying and treating the most complex of all life and of listening to the intimate struggles and problems of his fellow man. This is a privilege which must be cherished and closely guarded.

Four or more years of intensive training may cause the young surgical resident to become primarily concerned with the treatment of disease but less so with the treatment of patients with disease. He may develop a tendency to think of his patient as a perforated peptic ulcer or even a "vegetable" in ward bed L4, rather than a patient with financial, family, and social problems greatly compounded by his disease. By the same token, it must be remembered that the young surgical resident absorbs from his chief not only his scientific knowledge, his surgical judgment, and details of his surgical technique, but also his philosophy, his fundamental honesty, his character, and his attention to his patients' welfare and happiness.

It has always been desirable for the physician to have an idea of the time and place in which he lives, remembering the work already done by physicians throughout the ages. Specialization today has bred in some instances an individual who often is only a segment or one dimension of what an educated and cultured physician should be. Santayana said, "Those who cannot remember the past are condemned to repeat it," and this would seem to be particularly apt today.

Fragmentary records of man's civilization go back approximately 6,000 years. In each of the old fundamental cultures, including the Egyptian, Chinese, Hindu, Greek, Roman, Babylonian, Arabian, Mayan, and Mexican, a medical culture

developed and reached its climax. Usually its crystallization occurred in a large metropolis, the center of that culture, and its decline and death paralleled that of the culture, leaving only traces to be picked up by succeeding civilizations.

In studying primitive civilization it must be kept in mind that living forms from bacteria to man have tended to grow in colonies. Primitive people often had biologically correct habits, and their rules and rituals seemed to be directed toward protecting their food sources, their reproduction, and their social relationships. Colonies of human beings likewise sought those things which they thought would help them to avoid disease, pain, and death. Witch doctors constituted the most ancient professional class, and surgical procedures performed by them were often dictated by common sense. If a man broke his leg, it was often splinted empirically by the tribe's medicine man. This was rational surgery, and how much it was guided by the conscience is unknown.

In the long period of ancient Egyptian civilization, historians have revealed that a system of medicine was developed in which surgery had a respectable place, and in which the conscience undoubtedly reached a high level. Imhotep, who lived approximately 3150 B. C., was the first physician recorded in history. As a result of his contributions to Egyptian medicine and the care of his fellow man, the people made him a God of Medicine and invested him with the attributes of a deity.

About 2,000 years B. C. the ancient kingdom of Babylonia was founded, and Babylonian culture became both orderly and scientific. There were three classes of physicians: knife doctors, grass doctors, and conjuring doctors, who were the equivalents of our modern surgeons, internists, and psychiatrists. Curiously, only the surgeon was looked upon as a true physician, although his science was oriented in the direction of magic. Livers, sacrificially dissected from sheep, were used by the surgeon to fortell the future by hepatoscopy.

In ancient Greece the priests of Apollo and Aesculapius were the first surgeons, but they were replaced later by the philosophers, who began medical research and initiated the unification of medicine and surgery into an applied science. They looked at disease as a natural phenomenon, created a moral code for medical practice, thereby providing the first organized impetus to the surgical conscience, and established the physician and surgeon as individuals indispensable to human society. The first Greek philosophers were physicians, and it became important for them to remain morally and professionally free from reproach. The ideal physician of the Hippocratic period was individualistic, wise, humble, and humanitarian; he insisted upon the importance of treating not disease but the diseased. Our ideals today are very similar to those of Hippocrates from the point of view of morality and conscience.

The contribution of the Roman civilization to surgery was slight, since surgical practice was almost entirely in the hands of the Greeks. The expansion of the military might of the Roman Empire to achieve their ambition of world domination, made it expedient for them to borrow their medicine from the Greeks as a practical aid to survival. Medicine as a profession was beneath the dignity of the Roman citizen, and the first physicians were Greek slaves of wealthy Roman families. Although Julius Caesar extended citizenship rights in 46 B. C. to all foreign physicians in recognition of their service, the Romans inadvertently became responsible for the stagnation of medicine for more than 1,200 years, and proved that medicine can flourish only in a free climate. This made it possible for Galen, who was born about 130 A. D., to become the dictator of medical thought and to suppress the surgeon's conscience for more than 1,200 years. His word was the supreme authority, and to dissent from his opinions was heresy. Moral and political corruption followed by the barbarian invasion and malaria resulted in the final collapse of Rome.

During the Middle Ages, from about 500 to 1500 A. D., the Hippocratic traditions disappeared and medical knowledge regressed. Anatomy was forgotten, and professional medical codes of morals and ethics apparently did not exist. The medical profession became confined to the clergy. It was a period of continual struggle, horror, religious fanaticism, and contempt for the body and the rights of man.

Meanwhile, the Arabs in the fifth century A. D. carefully searched the Greek and Latin medical writings and continued the thread of humanism and romantic spirit. The Arabs hated the surgical knife, however, preferring the cautery in its place.

Near the end of the Dark Ages, European universities were established and grew from the passionate desire for knowledge that characterized medieval thought. In the 14th century, when barber surgeons were common and books on surgery and obstetrics were excluded from the Library of the School of Paris, Guy de Chauliac fostered the rebirth of interest in morality and the conscience and complied an outstanding text on surgery. He wrote, "Let the surgeon be well educated, skillful, ready, and courteous. Let him be bold in those things that are safe, fearful in those that are dangerous, avoiding all methods of evil practices. Let him be tender with the sick, honorable to the men of his profession, wise in his predictions, chaste, sober, pitiful, merciful, not covetous nor extortionate, but let him take his wages in moderation according to his work, and the wealth of his patient, and the issue of the disease, and his own worth."

Consider the conscience of Ambroïse Paré in 1537 when, by chance, he ran out of boiling oil, the agent which was universally considered best for the treatment of the wounds of the many injured soldiers suddenly committed to his care. Fortunately, he separated those who did not receive the boiling oil treatment in the firm belief they would develop malignant edema, gangrene, and death. The results spoke for themselves, and it was apparent that an immediate change in his ideas as to the "right" treatment was necessary.

Thomas Sydenham (1624 to 1689) established diseases as clinical entities and again emphasized the human aspect of medicine. He was a good, simple, and practical physician, who helped to revive the Hippocratic spirit of medicine and surgery.

Thomas Percival, born in 1740, maintained that everyone who entered the medical fraternity should agree to submit to the laws and to promote the honor and interest of the association insofar as they were consistent with morality and the general good of mankind. Wealth, rank, and independence, with all the benefits resulting from them, were the objectives he thought the young physician should hold in view, but knowledge, benevolence, and active virtue were of still higher estimation.

In 1823 the German physican, C. W. Hufeland, wrote a brief treatise entitled, "On the Physician's Power over Life and Death." He attempted to define the unique relationship that bound the patient to his physician, and, conversely, the physician to his patient. This relationship, based on confidence, dependence, and need of the patient on the one hand, and the skill, dedication, and conscience of the surgeon on the other was an integral part of a successful practice.

In the early part of the 19th century, the general public was duped by many medical cults existing throughout the United States. Their actions and the shortcomings of the medical profession in general were factors responsible for the cynical attitude of the public toward doctors. The practice of dissection and postmortem examination horrified the public. The physician, and particularly the surgeon, was often viewed with suspicion. The controversies and public quarrels among the members of the profession also undermined public faith. "It has become fashionable," wrote a contributor to the *Cincinnati Medical Observer* in 1857, "to speak of the medical profession as a body of jealous, quarrelsome men, whose chief delight is the annoyance and

ridicule of each other." How pertinent would be this comment today in some areas!

John Gregory, a brilliant member of the Edinburgh Faculty, also described his ideas of the duties and qualifications of the physician. He considered medicine to be a liberal profession, whose object was the life and health of the human species and a profession to be exercised by gentlemen of honor and ingenuous manners. He pointed out that the surgeon should not let professional quarrels and jealousies interfere with his patients' welfare. Those called in consultation should lay aside all resentments and think only of the patient. A surgeon should refuse consultation if he believes that he cannot act with good temper and sound judgment, but he should not refuse to attend merely because he does not approve of the requesting doctor's medical training or his ideas of treatment. Gregory's lectures thus pointed out a number of ideals which, when brought to consciousness in the surgeon's mind, motivated his action through his conscience. Quite ironically, Gregory's son, James, was the most flagrant offender of these ideals.

Before the advent of anesthesia it was the popular idea that a surgeon was a person who from the very nature of his calling was either unfeeling or cruel, if not actually brutal. At best, many believed that he was a callous man of indifferent sensibilities. It is quite evident that our surgical ancestor had to be possessed of great self-control in order that he would be able to perform heroic struggles against injury or disease by means of surgical operations. The conscious patient was held down by force, and the best surgeon was one who could accomplish his task in the matter of minutes with lightning strokes, amputating great masses of disease and dismembering the body. It is no wonder that operations were limited frequently to the exterior of the body and largely to results of war. In a single battle in the Russian campaign Dominique Larrey, Napoleon's great surgeon performed 200 amputations under such conditions. I have often reflected on the struggle he must have had with his conscience.

Consider the revolution in concept of what was the best surgical technique after the introduction of anesthesia in 1846-1847 and its result on the surgeon's conscience. The fast, rough, and often careless surgery was soon displaced by delicate, painstaking, and more meticulous technique.

Occasionally in the history of surgery, bitter conflicts have developed between men in their zeal to relieve human suffering. This has not been in the best interest of surgery and has often resulted in tragedy for the participants. For example, such a controversy as to who was the discoverer of surgical anesthesia and most deserving of the title "Benefactor of Mankind" arose among four men: two dentists and two physicians. As a result, this great discovery which has contributed so much to the alleviation of suffering and advancement of surgery has been tainted with greed, addiction, litigation, suicide, and tragedy. Wells, in his crusade to replace ether with chloroform as the anesthetic of choice, probably became a chloroform addict, and committed suicide in 1848, using chloroform to deaden the pain. Morton, who had dreamed of great wealth as the result of his discovery, was impoverished by the controversy. He neglected his practice and spent his time in search of fame until his death. Long, a physician, was embittered by the controversy and was left penniless at the time of his death in 1878. Jackson, who was a physician and a chemist, after taxing his mind and strength to the utmost in his battle against Morton, died in a mental asylum in 1880. Thus all four, who were guided more by the quest for fame than their conscientious treatment and relief of mankind, came to ruin and tragedy.

The 20th century brought an overwhelming rapidity of change. During the first part, the surgical conscience flourished and helped surgery reach its present high position. With scientific inventions and discoveries, the surgeon's conscience has become conditioned to the point that he is able

to give his patients the best surgical care in history. On the other hand, there has been evidence of disturbing changes in our values, our attitudes, and our points of view. What was once important and mandatory may now be considered trivial, optional, or expedient. It would seem that there is a trend to move from morals and conscience to morale and expediency.

As a result there is a tendency to develop standards which are not standards, to impose rigid regulations on the activity of surgeons, to follow limited professional crusades which are not crusades, to use operative procedures which have not been fully worked out, to follow popular demands in prescribing drugs and treatments in the face of inadequate or adverse clinical experimentation, to overlook the basic truths of wound healing, to become blindly reliant on antibiotic therapy, and to disregard the disciplines of asepsis and antisepsis. The progressive emergence of antibiotic-resistant staphylococci and the resultant world-wide problem of hospital-acquired infections are significant consequences.

From a professional point of view these trends threaten to reduce us to mediocrity. It would seem necessary for surgeons to learn to stand aside from the crowd, to think conscientiously and individually, to have the moral courage to protest, and to dissent from majority opinion when it is obviously in error. We cannot afford to bankrupt our philosophical heritage or surgical conscience.

Through the experimental method introduced by John Hunter, many new truths have been evolved. The extension of the experimental method to human beings without their consent by Hitler's Germany, however, was a cruel and unfortunate miscarriage of the conscience. It is difficult to understand how surgeons could have participated in the experiments described in the Nuremberg Military Tribunals. Although the defendent physicians generally argued that the medical experiments took place because of military necessity and the national emergency presented by war, it is obvious that no physician has the right to lower other human beings to the level of guinea pigs by force. This involves a fundamental contradiction to the duty of the surgeon, a violation of the dignity of the individual, and a presumption that could not persist without horrible results.

The English historian and sociologist, Thomas Carlyle, once said: "Your life—and were you the humblest of human beings—is not a wild dream, but a lofty fact." It is strange that such medical atrocities could have occurred in Germany, where the research efforts of earlier German doctors such as Robert Koch, Emil von Behring, Paul Ehrlich, and others in the last century saved so many human beings from serious and fatal diseases.

The emphasis during recent years has been on the needs of the common man and his happiness. It would appear that we need today more than ever the uncommon man and the uncommon accomplishment. The surgeon's dignity and freedom should be kept unblemished and above the numerous conflicts prevalent in the practice of medicine manifested by inconsequential group meetings, group selfishness, specialty groups, fragmentation of medicine due to competition for different areas and systems of the body, certificates of specialization, Boards and the like.

The population increase of the United States and the world is imposing added obligations on surgeons and surgery. Plans for meeting the needs of this increase in population are woefully inadequate. The present trend of specialization apparently will accentuate the inadequacy of our plans for the future. For example, should our concern be whether anesthetics will be given by the anesthesiologist or the trained nurse anesthetists or will there be enough skilled anesthesiologists and nurse anesthetists to meet the anticipated demand? The report of the governors committee of the American College of Surgeons stresses the importance of the latter. The unilateral direction taken by some of the specialty groups and Boards in surgery will almost certainly have its untoward consequences.

It reminds me of the lady riding in the plane who was told that one of the propellers had just stopped. She replied that she wasn't worrying since it was not on her side of the plane, anyway.

One of the conflicts in conscience encountered by the surgeon is of frequent occurrence—what should the patient with cancer, and particularly incurable cancer, be told. No one questions the right of the patient to know ultimately that he is going to die. He should have sufficient time to make spiritual and financial arrangements. Most surgeons today seem to prefer postponing telling the patient of the incurable state of his cancer until the late stages. In fact, the majority of families will specifically request that this information be withheld. The patient who knows that he has an incurable cancer is usually unable to be free of deep concern, be that for his family, wife, children, or business.

Should life be prolonged by heroic therapy in the hopeless patient who is obviously dying of cancer? One of the strong prerequisites of a good surgeon is his optimistic attitude, his hopeful treatment against seemingly insurmountable obstacles. For a surgeon to give up in the care of his patient, or to hasten the patient's demise, would be most difficult.

A surgeon's life is a difficult one at best, being one of endless strain, long hours, frequent deadlines, physical fatigue, and mental and emotional exhaustion. In the face of these, he must be able to continue to carry heavy responsibilities as they are thrust upon him and to maintain the same acuity of judgment and conscience. He must remain alert and vigilant, being concerned with the need for keen judgment in weighing the chances of life or death, the tolerance of the patient, and the advisability for indicated compromises instead of the "ideal" treatment. These questions are ever present, as well as the decision as to whether or not operation is to be done at all.

The appearance and personality of the skilled surgeon are generally known to his patients and acquaintances, but his surgical conscience, the emotional part of his nature distinguished from his scientific knowledge is part of his make-up that is relatively unknown. The deep emotions which agitate him and with which he is rarely credited, cannot be appreciated fully except by another surgeon who has experienced them.

Every conscientious surgeon must worry about his patients. "A man who doesn't worry at all, doesn't care a whole lot," said DaCosta, "and I should not want a man who does not care a whole lot to operate on me or mine." Perhaps worry is a device of the conscience to make him try to do his best, especially under unknown or unanticipated conditions. On the other hand, if he worries only because he may be sued in court, or his reputation may be damaged, the voice of his conscience is the fear of being caught. Unfortunately even a good surgeon today must expect harsh, unjust criticism, and the threat of malpractice liability is increasing.

It is interesting to note that the stressful life of the surgeon has suggested to some that a malign destiny was intervening in their affairs. This so impressed Pirogoff that he wrote an essay on "Luck in Surgery."

How can the surgeon remain human and insensible in this age of science and unsentimental practicability? As mentioned above, the surgeon experiences physical, mental, and emotional exertion during a difficult operation, and the very gravity of the circumstances in which he is placed absorbs all of his energy and diverts his mind from other preoccupations. These experiences are different, however, from the more deliberate evaluations of his work after the completion of the operation or after a tragedy. Then the self-imposed, heartless, incriminating cross-examination of the surgeon himself standing before his own conscience begins. He must ask himself what part of the disaster may be attributed to his own inadequacies or could have been averted. As Rudolph Matas

points out, "Happy is he who, listening to the voice of his conscience, shall hear her murmur in his ear the comforting words, which tell him that whatever his failures and shortcomings, he has done more good than evil; that on this earth where joy and misery travel side by side, his hands, though bloodstained not unlike those of the Saviour, have relieved more suffering than they have caused pain." Many misinterpret a surgeon's calm and undisturbed exterior as a disregard of suffering, or an indifference to human life, or would believe that the practice of surgery suppresses in the hearts of those who exercise it the qualities of sympathy and finer sensibility.

Today, insensibility and callousness are no longer necessary virtues in the surgeon but, quite the contrary, are characteristics to be avoided. There is no place for cruelty or indifference. Few realize the sickly sensations of the young medical student on witnessing his first surgical operation, and few surgeons outgrow the mental revolt occurring when they come face to face with the necessity of doing a mutilating operation on their fellow human beings. Their pity and worry over their patient's condition make it possible to share the burden of responsibility with the patient.

On the other hand, gentle compassion and tenderness do not exclude firmness and the necessity of making quick decisions. Resoluteness and an inflexible will often must be compatible with inexhaustible patience and sympathy.

A surgeon who has been addicted to alcohol or narcotics usually has been a failure. His inhibitions are weakened and judgment is blunted. He becomes boastful and impulsive although he may still be considered more or less sober. The finer demands of the surgical conscience may be lost in his resultant feeling of euphoria or antagonism.

Infirmity, disease, tremor of the hands, and impairment of judgment are the natural consequences of advancing age and the stress-life of the surgeon. They present a fateful and unavoidable condition which makes the aging surgeon less able to cope with the challenges offered by the seriously ill and injured. I have always been impressed with the self-imposed limitations of the older surgeons whose conscience leads them to refer the more difficult, time-consuming, and demanding operations to their younger colleagues or pupils.

The price of pain and grief in the surgeon's professional life is immeasurable. I will never forget my thoughts when a young mother of 28 years developed a cardiac arrest during cholecystectomy about ten years ago. We were able to reestablish the cardiac rhythm, but the patient never regained consciousness, dying 37 days later. Not long ago, I met the mother of this patient and the young daughter, who had been a baby at the time of her mother's death. The pangs of remorse were as acute ten years later as they were on the day of the operation.

Let us not forget that throughout the ages, truth and falsehood, good and evil, honesty and dishonesty, innocence and guilt, and the charlatan and the imposter have traveled side by side. Unfortunately, the busiest men in surgical practice are frequently not the best trained or the most capable. A large percentage of operations, particularly those which are ill-advised and unsafe, is done by the untrained or those outside our profession.

From these and other considerations it is apparent that the evolution of the surgical conscience has been characterized by recurrent conflicts between the traditional and dogmatic authority on the one hand, and creative thought and the scientific experimental method on the other.

The surgical conscience has not been static but dynamic, depending upon basic contributions to medical science, and sociologic or moral changes brought on by war, religion, government, and geography.

It would appear that our surgical conscience is now at an all-time high level, but that it is being challenged by many factors operating in our civilization today, principally within the medical profession itself.

There is even evidence of its deterioration.

History has shown that the surgeon's conscience has been a conditioned attitude of mind which has served as his compass, giving him direction for his efforts and guiding him correctly in the medical care of the people, particularly through political storms and difficult periods in man's recorded civilization. It has been in fact the "surgeon's soul" which, conditioned by the knowledge and problems of his time, has motivated him in search of the best treatment for the patients under his care. Rigid regulations, laws and dictatorial authority have failed as substitutes, and even have suppressed it. May we be fortunate enough to use our surgical conscience wisely for the solution of the many current problems behind the unrest existing in surgical practice and education today.

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Experimental Hemorrhage

Prediction of Mortality Following Acute Measured Hemorrhage in the Dog

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Introduction

Heretofore, studies of the effects of hemorrhage on animals have been inextricably associated with studies of shock. A few workers have reported experiments in which the independent variable was the loss of varying volumes of blood,[1,2] but their goal was either to produce or to elucidate some mechanism of shock. Walcott[1] determined the blood volume of dogs by means of Evans blue (T-1824) and the centrifuged hematocrit. These dogs were bled from their femoral artery 41% to 58% of their measured blood volume. He found that all animals died when bled 53% or more of their blood volume. Roughly 50% of the animals bled a smaller per cent of blood volume survived. In a later paper, however, Walcott[3] states that bleeding an animal according to a fixed percentage of blood volume is an unreliable means of producing shock. Thereafter, Walcott used a modification of Mann's[4] "bleeding volume" as an index of the volume of blood loss required to produce a picture of shock. Mann[4] placed a large cannula in the femoral artery of a dog and allowed blood to flow out until it spontaneously stopped. Then he rapidly opened the dog's chest and collected the volume of blood that spontaneously spilled out of the right atrium. He defined the "bleeding volume" as the sum of the two volumes collected. Wang et al.[2] bled animals a fixed proportion of their measured blood volume to determine whether the mean lethal hemorrhage of normal etherized animals was different from the mean lethal hemorrhage of traumatized animals. (It was different; the injured animals tolerated less hemorrhage.) Others, notably Werle and Wiggers,[5] used hemorrhage in a different way to produce hemorrhagic shock. Their method involved rapid bleeding of an animal sufficient to achieve and maintain an arbitrarily fixed arterial pressure over an arbitrarily fixed interval of time. This method, then, used hemorrhage *as a means of achieving controlled hypotension,* and thus is a study of the effects of hypotension induced by bleeding rather than a study of the effects of bleeding per se. Such uses of hemorrhage in animals have led to important information concerning the pathogenesis of irreversible shock, but have left unanswered many of the simpler questions concerning the effects of uncomplicated, acute hemorrhage.

The work reported here is not intended as a study of shock. We are studying the effects of acute hemorrhage in the splenectomized dog, hoping to learn more about the effects of acute hemorrhage in man. We have chosen to study the splenectomized dog for several reasons: 1. The spleen of the dog is the source of a variable autotransfusion which tends to reduce the reliability of an estimate of mortality. 2. The human spleen does not

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function as a great source of autotransfusion. 3. Reeve[6] has shown that a blood volume determination in the dog with the spleen intact is uncertain unless both plasma and the red cells are tagged. The splenectomized dog, therefore, is more easily studied and is more similar to man than the unsplenectomized dog.

In the experiments we wish to undertake, it is desirable to be able to predict in advance of the actual experiment what the mortality of a given group of hemorrhaged animals will be. It might be desirable, for example, to subject a group of animals to an acute hemorrhage which would uniformly yield a high mortality, a 50% mortality, or a low mortality, depending on the information one wishes to gain. It is important, then, to know what index for hemorrhage will allow the most accurate mortality prediction. Should one bleed on the basis of a certain number of cubic centimeters per kilogram (cc/kg.) of body weight, the percentage of actual blood volume, or, from knowing the blood volume, bleed the animal to such an extent that he would have a certain number of cc/kg. of blood remaining in his vasular tree? This, then, is the crucial question we wish to answer in this paper: "What antecedent information would give the most reliable estimate of the probability that a given animal would or would not survive an acute hemorrhage of a certain volume?"

The work of others was of considerable aid to us in defining the range of the present work, even though other workers have used animals with spleens intact and have used either unanesthetized animals or anesthetics that were different from the one we used. Walcott and Wang[7] found that the bleeding volume of animals with spleen intact was about 60% of their blood volume. Deniz and Gregersen[8] found that the "bleeding volume" for splenectomized animals was about 46% of their total blood volume, and that anesthesia had little or no effect on the bleeding volume. Walcott[1] had 100% mortality in a small group of animals with spleens intact which were bled 53% of their blood volume or more. From the above data, then, one would estimate that 100% mortality in the splenectomized, anesthetized dog would be in the range of 45% to 50% of his blood volume. Wang et al.[2] determined the blood volume of animals before hemorrhage and one to two hours after hemorrhage. They found that the mean lethal hemorrhage (L. $H._{50}$) was 37.4% of the original blood volume, when this is computed as being the per cent which the second determination is less than the first. Since it is known that hemodilution occurs following acute hemorrhage,[1] it is reasonable to assume that the mean lethal hemorrhage expressed simply as a percentage of the original blood volume would be somewhat greater than 38%. Previous work from this laboratory[9,10] has shown that splenectomized, anesthetized dogs survive a hemorrhage of 35% of their original blood volume.

From the above we estimated that the splenectomized animal under pentobarbital anesthesia would withstand a hemorrhage of 35% of its blood volume, that a 50% blood volume hemorrhage would result in 100% mortality, and that the mean lethal percentage of blood volume hemorrhage would be somewhat above 38%. A preliminary report on the work of this paper has been presented previously.[11]

Methods

All dogs were splenectomized with use of sterile surgical technique. After the procedure, each animal was placed in a separate cage and fed a routine diet for at least 30 days prior to the actual bleeding experiment. Owing to the 30-day interval between surgery and the experiment, we feel confident that all of the animals reported here were in good health and in a steady nutritional state.

Data are reported here on 74 animals. Group I consists of 34 animals bled 35% of their measured blood volume. These animals were used as controls for experiments previously reported[9] and are given here only to lend precision to our estimate of the relationship between per cent of blood volume hemorrhage and mortality. Group II consists of 40 animals of over 10 kg. of body weight.

The following is a description of the treatment of Group II.

In the afternoon of the day before the experiment, food was removed from the animal's cage and water left ad libitum. In the morning of the experimental day, the animal was anesthetized with I. V. pentobarbital (30 mg/kg.). With use of aseptic technique, the right femoral artery and the left femoral vein were cannulated by large-diameter polyethylene tubing. The mean femoral arterial pressure was monitored continuously by means of a mercury manometer. The animal was left in this state for at least one hour and until his arterial pressure had not varied more than 10 mm. of mercury for a 30-minute period. After this period of stabilization, which varied between one and three hours, the animal's blood volume was determined by radioactive iodinated human serum albumin (RIHSA) from a single 10-minute sample as described elsewhere.[13] Within 15 minutes of the blood volume determination, the bleeding was begun. An animal was bled a specific volume between 35% and 45% of his measured blood volume. The bleeding was done from the femoral arterial cannula and was completed in from three to five minutes. After the bleeding the animal was observed for several hours. If he survived this initial period, he was returned to his cage. He was presented with no food or water until the next morning. To be classified as a survivor, the animal had to be alive seven days later. Of these animals, 15 were artificially ventilated for four hours beginning immediately after the hemorrhage. An earlier preliminary report[11] has shown that this procedure does not influence the relationship between per cent of blood volume hemorrhage and the per cent mortality. Roome et al.[18] have also shown that hyperventilation does not influence bleeding volume. Therefore, no distinction has been made in this paper between those animals given artificial respiration and those with unassisted respiration.

Results

The complete data on Group II are presented in the Table. The animals are listed in the order of increasing per cent of blood volume hemorrhage. In addition, the animal's weight, prehemorrhage blood volume, hematocrit value, and the result of the hemorrhage are tabulated. From these data, all of the analyses made here can be derived. The other information available is the fact that 34 dogs (Group I), which were bled 35% of their blood volume, survived.

Data on Seventy-Four Animals Bled a Measured Per Cent of Their Original Blood Volume

Group I Animal No.	% Bld. Vol. Hem.	Result
1-34	35%	All living

Group II Animal No.	Kg. Wt.	Prehem. Bld. Vol.	% Bld. Vol. Hem.	Hct.	Result
35	20.6	1,712	39	47.0	L
36	22.6	2,090	39	46.5	L
37	17.0	1,371	39	46.5	L
38	14.5	1,255	39	44.5	L
39	23.6	1,701	39	41.5	L
40	18.6	1,395	39	48.2	L
41	10.7	1,006	39	44.3	D
42	20.0	1,768	39	45.6	L
43	11.8	1,033	39	26.8	D
44	16.6	1,384	39	40.9	L
45	15.2	1,268	40	47.0	L
46	21.0	1,683	40	45.5	L
47	14.2	1,377	41	44.8	L
48	11.0	836	41	43.2	L
49	17.0	1,568	41	47.1	D
50	16.5	1,480	41	44.8	D
51	16.0	1,424	42	48.0	L
52	23.0	1,769	42	40.4	D
53	12.0	1,274	42	39.6	D
54	15.9	1,444	42	44.2	D
55	11.4	1,186	42	47.5	D
56	20.0	1,816	42	42.1	D
57	13.6	952	42	42.0	L
58	15.4	1,162	42	21.2	D
59	16.8	1,779	42	39.9	L
60	13.2	1,042	42	23.4	D
61	18.2	1,474	43	48.5	D
62	10.1	819	43	30.7	L
63	16.0	1,797	43	39.7	L
64	11.0	1,232	43	46.4	D
65	11.2	1,151	44	50.0	D
66	11.0	1,055	44	50.2	D
67	14.5	1,409	45	42.5	D
68	19.5	1,571	45	42.8	D
69	12.7	893	45	45.0	D
70	10.4	1,021	45	37.1	L
71	22.7	2,106	45	47.4	D
72	16.4	1,417	45	46.7	D
73	20.5	1,931	45	31.9	D
74	20.4	2,220	45	46.3	D

Analysis of Results

Many investigators have bled animals on a cc/kg. basis. Figure 1 illustrates the crudeness of the relationship between cc/kg. hemorrhage and mortality from the data of the Table. The abscissa is the number of dogs. Those animals to the left of zero survived, and those animals to the right died. It is apparent that bleeding animals by the index of cc/kg. of body weight does not allow one to predict whether a group of animals will live or die after a hemorrhage

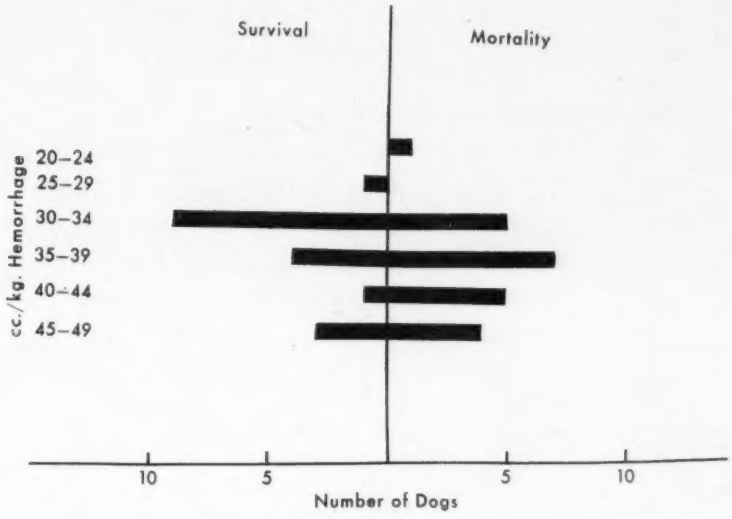

Figure 1

of a certain volume. This confirms the experience of all who have approached the problem in this way.

It would seem reasonable that an animal's survival might be better related to the number of *cc/kg. of blood left in the animal* after hemorrhage. Figure 2 illustrates the relationship between the cc/kg. of blood remaining in the animal and the mortality of the bleeding. The values on the ordinate were calculated as follows: The volume of blood removed from the animal was subtracted from the total blood volume of the animal before hemorrhage; the remainder then was divided by the number of kilograms of body weight. Note that there does seem to be some separation in the rates of mortality at about 52 cc/kg. Certainly,

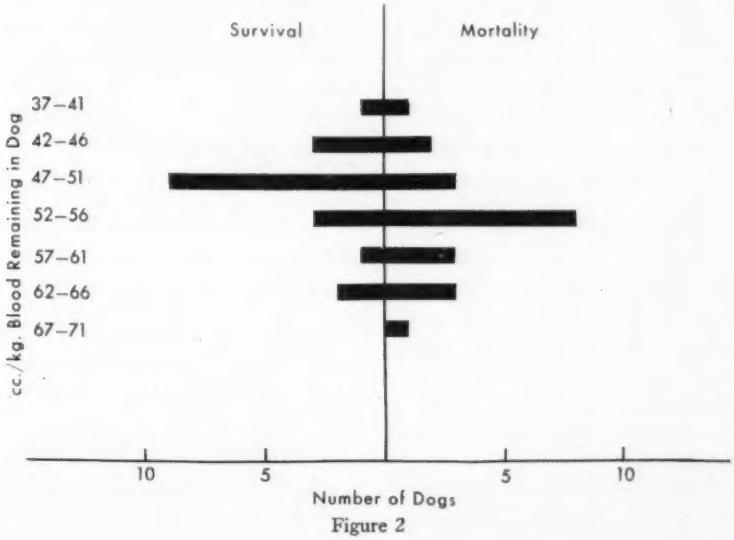

Figure 2

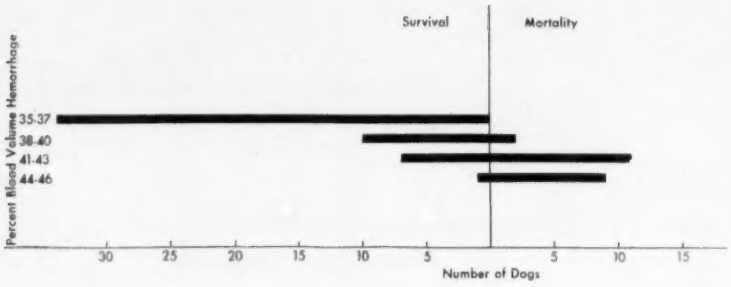

Figure 3

bleeding a larger volume so that less blood than this remains in the animal leads to a greater than 50% mortality, and, conversely, bleeding a smaller volume leads to a mortality that is considerably less than 50%. However, the predictability is very crude.

On the other hand, the predictability of mortality is considerably improved when per cent of measured blood volume is used as the index of hemorrhage. Figure 3 illustrates such data from the Table depicting the relationship between the per cent of blood volume hemorrhage and mortality. This figure shows immediately there is a progressive mortality as the per cent of blood volume hemorrhage is increased. No animals died following a 35% of blood volume hemorrhage; 50% mortality is somewhere between 41% and 43% of blood volume hemorrhage, and the majority of animals bled 45% of their blood volume die.

Figure 3 shows that there is a good correlation between the per cent of blood volume hemorrhage and mortality, but such a treatment of these data does not permit a precise mathematical statement of the relationship found even in this sample. Neither does such a treatment allow any statement concerning the probability that all animals, treated as those reported here, will respond in the way that this sample of animals has responded. For the design of future experiments, we wish to be able to state a definite value for the *mean lethal hemorrhage* (L. $H._{50}$), and, further, to be able to state quantitatively what degree of confidence can be given to this value. It might be equally valuable to know the L. $H._{20}$ or L. $H._{80}$ and their confidence limits. The method which seems to us to be best suited to achieve these ends is that of probit analysis as described by Bliss.[14] Figure 4 illustrates the data of Groups I and II. The percentage mortality of each of the three groups in Figure 3 in which there was a mortality has been converted into probits * by reference to a conversion table in Fisher and Yates,[15] and appears on the graph as a dot. Since a probit can only approach zero but cannot achieve it, the group of animals with zero mortality is plotted as an arrow pointing in the direction of influence on the regression line at the appropriate position of the log of the independent variable (log 35%=1.526). The probit conversion merely changes a normal distribution curve into a more convenient linear scale. In essence this conversion of the ordinate partially straightens the sigmoid curve seen on rectangular coordinate plot. The abscissa of Figure 4 is the log of the per cent of blood volume hemorrhage. Bliss recommends using the log of the independent variable since most all-or-none phenomena are skewed toward the 100% result of the dependent variable. This maneuver further straightens the sigmoid curve, in fact to such an extent that it can now be subjected to statistical evaluation. The solid line drawn on Figure 4 is the

* A probit is defined as the Gaussian value plus 5.

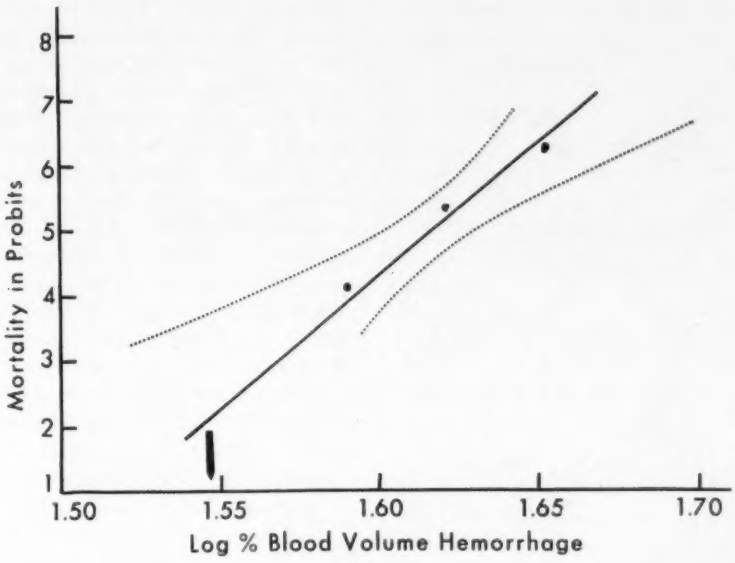

Figure 4

calculated regression line of these data. The equation for this line is $Y=54.62+36.86\ X$. From inspection it is easily seen that the plotted points from the experimental data do not deviate from the calculated regression line appreciably. The χ^2 test for fit of the data to the regression line yields $0.5>p>0.3$, which confirms the impression gained from inspection that the scatter of the data around the regression line can be accounted for by random sampling. The two curved lines indicate the 95% confidence limits of the regression line. Thus, there is only 1 chance in 20 that the true regression line of all animals in such an experiment will lie outside these limits. In other words, this index allows 95% accuracy in predicting mortality in any group of animals bled a per cent of their blood volume between 35% and 45%.

Comment

We have shown that a reliable estimate can be made of the probability that a dog will survive or die after an acute hemorrhage of a known per cent of the measured blood volume. There are several requirements necessary to achieve this end. By removing the spleen prior to operation, a variable source of autotransfusion is avoided. An interval following splenectomy is important. Splenectomy immediately followed by the experimental hemorrhage would be useless because of the known effect of surgery on an animal's tolerance to hemorrhage. It is important that the animals be free of disease. The practice of performing survival experiments on animals recently arrived from a dog pound is deplorable. This procedure invariably places some animals in the dead column for reasons other than the experiment. In addition, it is important to know that the animals are in a good state of nutrition prior to the experiment. For the above reasons, the animals reported here were splenectomized under sterile conditions shortly after their arrival in the laboratory. After the surgical procedure, the animal was placed in an isolated cage and fed a routine diet for at least 30 days before the experiment. The value of this sequence was demonstrated to us by several animals which died of distemper within the first postoperative week.

It is also critical that the animals be in a steady and comparable state of anesthesia at the time of the blood volume determination and throughout the remainder of the experiment. This is of importance for two reasons, namely, the lability of the blood volume with a fluctuating arterial pressure, and the poor response of an animal to hemorrhage when overly depressed by anesthesia. Price et al.[16] have shown that the cardiovascular system of the dog under pentobarbital anesthesia requires from one to three hours for stabilization, but after a steady state has been achieved, it remains in this state for hours. The one to three hours for stabilization corresponds to our own experience.

With the above factors adequately controlled, there is a useful correlation between the per cent of blood volume hemorrhage and mortality. The mean lethal hemorrhage (L. $H._{50}$) is 41.6% with the 95% confidence limits of 40.1% to 42.7%. The L. $H._{80}$ is 43.6% with 95% confidence limits of 42.3% to 46.3%. The L. $H._{20}$ is 38.8% with 95% confidence limits of 36.9% to 40.6%. Note that the greatest confidence can be ascribed to the L. $H._{50}$ and decreases toward each end. However, in certain experimental designs, it might be more efficient to use the L. $H._{20}$ or L. $H._{80}$. For example, if one wishes to determine the therapeutic effect of an agent, a saving of animals could probably be made by bleeding the control and test groups at the L. $H._{80}$ level. This would give a wider range for the therapeutic effect to demonstrate itself.

One might assume that the lack of correlation between the cc/kg. hemorrhage and mortality is due to the wide range of the normal blood volume in dogs when expressed in cc/kg., and that such a hemorrhage might represent a large blood loss to an animal with a small cc/kg. blood volume, or a small blood loss to an animal with a large cc/kg. blood volume. This might lead one to the opinion that the important factor is the number of cc/kg. of blood not removed from the dog. Indeed, the correlation, as plotted in Figure 2, is an improvement over Figure 1. However, the relationship is not a very good one. One might expect the relationship to be improved somewhat if lean body mass were the denominator rather than the total body weight, but we have no such data available.

There is another theoretical approach to the problem. The normal blood volume of the dog is the normal volume of the animal's cardiovascular system. Since the normal range of blood volumes in terms of cc/kg. is wide, it follows that the normal volume of the cardiovascular tree is equally variable in relation to the animal's body weight. This is shown pictorially in Figure 5, where, for purposes of illustration, equal blood volumes and hence equal volumes of cardiovascular tree are shown in the bodies of various-sized animals. The important relationship, therefore, is that between blood loss and the size of the vascular system, rather than blood loss and the volume of the animal. The data in this experiment lend support to this theory.

Thus, the per cent of blood volume hemorrhage is indeed a potent determinant of mortality in the splenectomized dog. However, we do not wish to imply that this is

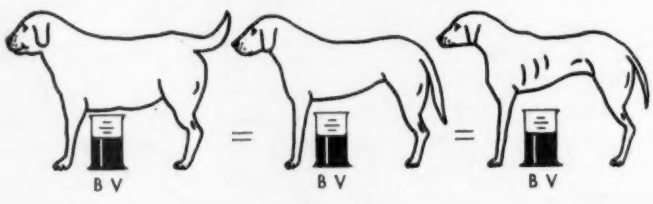

Figure 5

the only good determinant that can be calculated prior to bleeding. It would seem, a priori, that the hematocrit would be an important factor at any level of bleeding. One might logically assume that the animal with a low hematocrit would be less likely to survive a given per cent of blood volume hemorrhage than an animal with a normal hematocrit. The Table shows that three of the animals of the present series had extremely low hematocrit—21.2%, 23.4%, and 26.8%—for reasons that were not apparent. All three of these animals died, even though we would have predicted that only one of the three would die. No statistical evaluation, however, can be made on the basis of only three dogs.

Another crude estimate of the influence of the hematocrit can be made by a comparison of the means of the hematocrits of those animals which died with those that lived. These means are 41.9 and 43.3, respectively. Again, the differences are in the proper direction of the assumed effect of the hematocrit, but are not statistically significantly different. If we compare the hematocrits of surviving and dying animals which have been bled a percentage of blood volume hemorrhage that should give the animal about a 50-50 chance of survival (41%-42%), we find a living mean of 43.6% and a dying mean of 38.9%. But again, with samples of this size, the differences are not statistically significant. On the other hand, the animals which survived 43% or greater of blood volume hemorrhage had a mean hematocrit of 35.8% and those which died had a mean hematocrit of 45%. It is obvious, then, that the question of the influence of the initial hematocrit on mortality must remain open until an experiment is designed to determine this influence. The data in this report do not permit a definite statement of effect or lack of effect, but it would seem that the initial hematocrit, if within normal range, is probably not an important factor. The most potent factor in mortality seems to be the per cent of blood volume hemorrhage.

Summary

A standard experimental preparation to study acute hemorrhage is presented. This consists of a splenectomized healthy dog under pentobarbital anesthesia. A high degree of predictability of mortality rate can be achieved when bleeding is based on a specific per cent of measured blood volume. The L. $H._{50}$ with this preparation is 41.6%. Various facets of this experiment are discussed.

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Bacterial Studies in Irreversible Hemorrhagic Shock

W. R. CULBERTSON, M.D.; WESLEY ELSTUN, M.D.; WILLIAM COLE, M.D., and W. A. ALTEMEIER, M.D., Cincinnati

The studies of Fine and his co-workers suggested that a bacterial factor was a cause of irreversibility of prolonged hemorrhagic shock in experimental animals and that the defense mechanism against this factor could be enhanced by the preliminary administration of certain antibiotics, principally chlortetracycline (Aureomycin).

Fine et al.[1] had reported dramatic and interesting data which they interpreted as indicative of a bacterial factor being important in the production of "irreversible" hemorrhagic shock in dogs. Their conclusion was based in part upon the finding that the survival rate in their experiments with a standardized challenge by hemorrhagic shock was significantly increased by the preliminary administration of certain antibiotic agents. Other workers, notably DeBakey,[2] were unable to demonstrate this protection or to demonstrate any significant difference in mortality between the control group and the group treated with antibiotics. The detection of the nature and method of action of bacterial factors involved would permit hope of development of methods to prevent many deaths in such clinical fields as massive trauma, severe internal hemorrhage, and nontraumatic diseases causing profound and prolonged shock.

The following represents the material, methods, and results of the experiments done on this aspect of the problem in the Department of Surgery of the University of Cincinnati. In the initial study, attempts

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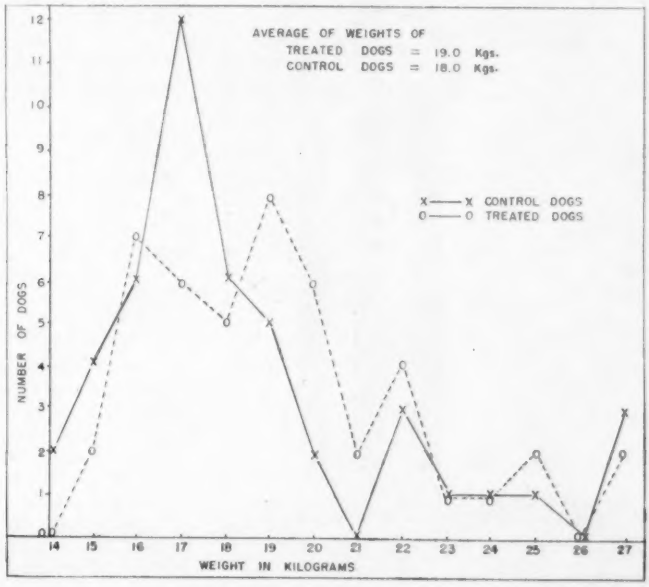

Fig. 1.—Comparison of weights of control and treated dogs (Group 1).

were made to duplicate the methods described by Fine as nearly as possible.

Material and Method

Healthy mongrel dogs, weighing from 13.9 to 27.3 kg. were used as the test animals and were held in our kennels for at least one week prior to challenge. During this time they were examined for evidence of concurrent infection or disease and a satisfactory state of health and nutrition. Infestation with heart worms has not been observed in these animals.

All animals, both control and treated, were subjected to hypovolemic shock produced by the controlled-hemorrhage technique of Fine. In the more recent aspects of this study minor modifications of his method have been used. All animals in our studies were paired, one of the pair being used as a control and the other being treated by an antibiotic agent for a period of days prior to challenge, including the day of challenge. The technical details of the method were as follows:

The dogs were restrained in a supine position by means of ties on each extremity. Two hours after the administration of ½ grain (30 mg.) morphine sulfate hypodermically, the femoral vein and artery were exposed and cannulated under local procaine anesthesia. Heparin, 50 mg., was injected into the vein. The femoral artery was then connected to a system containing a Lamson bottle reservoir and a mercury manometer. The Lamson bottle reservoir contained 50 mg. of heparin. All tubing, cannulae, the reservoir, and the manometer were clean but not sterilized (in accordance with Fine's method). The system was then opened, and the animal was allowed to bleed spontaneously into the reservoir. By regulating the distance of the reservoir above the level of the animal's heart, the hydrostatic pressure could be modified to regulate and maintain the animal's blood pressure between 30 and 40 mm. of mercury as measured on the manometer. With this arrangement the animal could shed or reabsorb its blood as its homeostatic mechanisms indicated, but could not elevate its arterial pressure above the level described. As soon as shock levels were reached, the four restraints on the extremities were loosened and the animal was turned slightly on his side to facilitate breathing. The system was allowed to remain open, and the reservoir was observed to determine the maximum quantity of blood lost by the animal. After a period of minutes, usually 20 to 30, the amount of blood shed into the reservoir reached the maximum. This quantity was called the "maximum bleed-out." Subsequent to this, the animal began to reabsorb the blood in the reservoir bottle and when it had reabsorbed 40% of the "maximum bleed-out" the challenge was terminated by the transfusion of the remainder

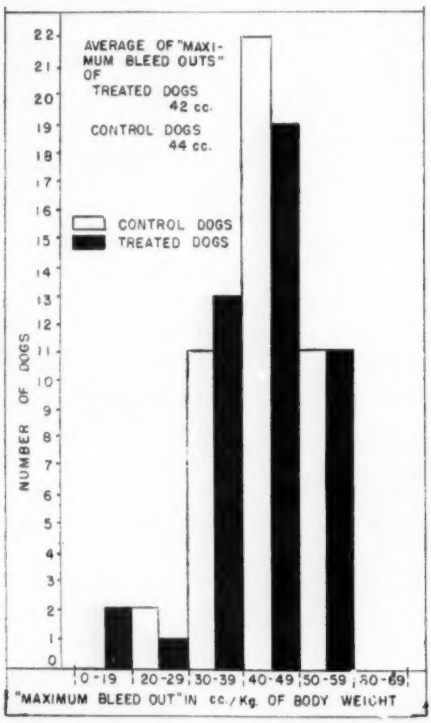

Fig. 2.—Comparison of "maximum bleed-out" (in cubic centimeters per kilogram) of control and treated dogs (Group 1).

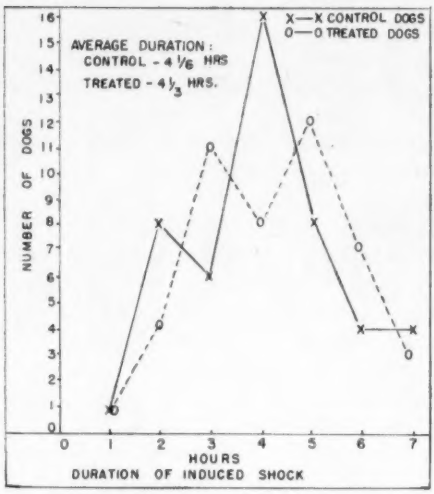

Fig. 3.—Comparison of duration of induced shock in control and treated dogs (Group 1).

of the blood in the reservoir by the intravenous route. Reabsorption of 40% of the "maximum bleed-out" usually occurred within four hours of the start of the experiment. The femoral artery and vein were then ligated after removal of the cannulae, and the wound was closed. The animals were then returned to their cages.

Before challenge with this form of hemorrhagic shock, the paired animals were divided into two main groups, a control group and a group prepared by treatment with one of the broad-spectrum antibiotics. Each treated dog was paired with a control animal. Each treated animal received by gavage 5 gm. of chlortetracycline daily for four days prior to challenge and either 500 mg. of the same drug intravenously on the day of challenge or 5 gm. by gavage two to three hours prior to hemorrhage. In all other aspects the challenge described above was identical in the control and treated animals.

In the *first phase* of this study, there was no particular attempt made to achieve asepsis in technique. As in the studies of Fine, the apparatus, equipment, and instruments used were only washed, cleaned, and reused on other dogs without any attempt to establish sterility.

Results

Resistance to this challenge was considered successful if the animal survived 48 hours or longer. By this method, 92 animals were challenged, 46 being treated with the antibiotic and 46 being untreated controls.

The average weight of the treated animals was 18.0 kg. and of the control animals, 19.0 kg. The distribution of the animals among the various weights is shown in Figure 1. This indicates that the sizes of the dogs in the two groups were closely comparable.

The "maximum bleed-out" is a factor in the severity of challenge when calculated in number of cubic centimeters per kilogram of body weight for each animal. In Figure 2 these data are given. The distribution of the animals in each of the groups is closely comparable for the treated and control animals. This indicates that one measurement of the degree of challenge of the control dogs can be compared closely with that of the treated animals.

Another measurement of the severity of challenge is the period of time between initiation of hemorrhage and termination of the induced shock (40% take up). In Figure 3 the curves indicate that the distribution of the animals along the times required for termination of hemorrhage are similar enough for accurate comparison of control and treated groups.

The average initial arterial blood pressure for the control animals prior to bleeding was 140 mm. Hg, the highest being 200 and the lowest 110. The average for the treated dogs was 142 mm. Hg with a high and low of 170 and 100 respectively. From these observations it is apparent that the 46 treated animals and the 46 control animals received a closely comparable challenge.

Of the 92 animals studied in this series, there was no significant difference in the survival rate of those treated with chlortetracycline and the untreated controls. Of a total of five survivors, two had been treated with chlortetracycline and three had not. The surviving animals occurred at random in the course of the experiment, and the pertinent data show no deviation from the average to indicate the reason for survival. In Table 1 the significant data concerning all of the dogs who survived in this series are given.

Because of the suspected importance of bacteria in the occurrence of irreversibility in this type of hemorrhagic shock, routine blood cultures were done on the above animals before and during shock. The following results were obtained:

1. All blood cultures of the 46 control animals were positive.
2. All blood cultures of the 46 treated animals were positive.
3. All blood cultures of the surviving animals were positive.
4. An average number of three bacterial strains per animal were found in the antibiotic-treated and untreated animals, including the survivors.
5. A wide variety of bacteria were recovered from the blood streams of these animals.
6. The presence of Pseudomonas aeruginosa was noted in the majority of the cultures.

Further studies indicated that many of these bacteria were relatively resistant to chlortetracycline and that their sources

TABLE 1.—*Animals Surviving Challenge*
(Group I)

Dog No.	Date	Weight, Kg.	Maximum Bleed-Out Cc/Kg.	Duration of Induced Shock, Hr.	Initial Blood Pressure Mm/Hg.
Control Group					
548	2/22/55	18.0	46	4	150
276	1/17/56	20.0	35	5	*
282	1/24/56	18.0	54	6	*
Chlortetracycline-Treated Group					
544	2/22/55	17.0	30	4	160
273	1/17/56	18.0	39	4	140

* Not recorded.

were the clean but unsterile Lamson bottles and the rubber tubing connected to the femoral artery. Bacterial counts of the blood cultures indicated that the number found varied between 2 per cubic centimeter to more than 1,000,000 per cubic centimeter.

The above observations indicated that an appreciable amount of the dog's blood volume had been contaminated and infected by the bacteria in our laboratory environment and then retransfused to produce a severe and mixed bacteremia.

The *second phase* of the study was then undertaken to repeat the experiments completely aseptically so that the factor of contaminating bacteria peculiar to our laboratory could be studied as a possible cause for the failure of chlortetracycline to increase the rate of survival after this form of hemorrhagic shock. This was accomplished with considerable difficulty since no method of sterilization except by autoclave successfully sterilized all of the equipment. All instruments, bottles, tubing, cannulae, gauze, suture material, mercury manometers, etc., were subjected to this type of sterilization. Reservoir bottles were autoclaved at 20 lb. of steam pressure for 30 minutes on two successive days. Manometers were treated to 20 lb. of steam pressure for 30 minutes, and linens received sterilization by 17 lb. for 20 minutes.

Analysis of these results suggests that (1) the bacteria found in the blood cultures of the 92 animals in the first phase of the experiment were contaminants from the unsterile equipment and air of the laboratory; (2) these contaminants could be excluded completely from the experimental system; (3) when the contaminants were excluded, the blood cultures before, during, and immediately after shock were sterile, and (4) in the absence of bacteria in the arterial and venous blood, heavy chlortetracycline therapy administered before challenge, did not increase the survival rate or show any ability to reverse the irreversibility of the shock process.

The operative portion of the experiment was done under strict asepsis with sterile

TABLE 2.—*Animals Challenged Aseptically*
(All Blood Cultures Sterile)

Dog No.	Date	Weight, Kg.	Maximum Bleed-Out, Cc/Kg.	Duration of Induced Shock Hr.	Initial Blood Pressure Mm/Hg	Arterial and Venous Blood Cultures
Control Group						
558	3/ 6/56	19.5	38	4	120	Sterile
479	3/13/56	14.3	55	3	130	Sterile
496	3/20/56	15.0	41	4	130	Sterile
507	3/27/56	17.7	45	2	115	Sterile
571	4/24/56	21.0	38	1	150	Sterile
	Average:	18.0	44	3	129	
Chlortetracyline-Treated Group						
446	3/ 6/56	18.6	62	4½	130	Sterile
480	3/13/56	20.7	58	3	130	Sterile
498	3/20/56	16.8	71	4	120	Sterile
513	3/27/56	18.2	58	5	100	Sterile
555	4/24/56	19.3	58	4	*	Sterile
	Average:	19.0	62	4	120	

* Not recorded.

drapes, gown, gloves, masks, etc. The success of this modification of the challenge was measured by the demonstration of sterile arterial, reservoir, and venous blood cultures prior to and throughout the entire period of challenge. Attempts were made to grow bacteria by culturing the blood on at least five different media both aerobically and anaerobically. *All* of the cultures from *all* of these animals were sterile. Ten dogs were studied in this manner, five being controls and five having been treated with chlortetracycline. In Table 2 the data of this phase of the experiment are recorded. These data demonstrate comparable challenge of paired control and treated animals within the series and sufficient similarity to compare results with the initial series in which there was no asepsis. All 10 animals in this series died.

Summary and Conclusions

Duplication of Fine's experiments in irreversible hemorrhagic shock in our laboratory has not revealed any protection against death from such shock in dogs by the use of chlortetracycline (Aureomycin).

Secondary contamination by environmental bacteria may vary from massive to minute doses when the method used lacks complete technical asepsis.

Challenge of the animals under completely aseptic conditions does not influence the survival rate in either control or treated animals.

Bacteriologic studies indicate that any whole bacteria present in irreversible hemorrhagic shock in dogs are contaminants mechanically introduced in the course of the experiment rather than a manifestation of decreased physiologic barriers to their entry.

Cincinnati General Hospital (29).

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DISCUSSION

ON PAPERS BY DRS. SWAN, BLAVIER, MARCHIORO, JENKINS, AND MONTGOMERY, AND BY DRS. CULBERTSON, ELSTUN, COLE, AND ALTEMEIER

DR. HENRY SWAN, Denver: The preparation that has been described has now become sufficiently standardized so that there is a very high predictability in regard to the outcome when one bleeds in terms of the initial measured blood volume. Thus, if you want to study fluid shift under various conditions, if you want to study the effect of drugs on mortality rates, this preparation we think will be ideally suited for you, and is one in which you can rely statistically on the outcome in groups as small as 8 to 10.

So, we do hope that those of you who are interested in studying the effect of hemorrhage on animals will find this is a good way to do it.

DR. WILLIAM A. ALTEMEIER, Cincinnati: I believe it is of some interest to realize that these experiments were also duplicated in part in Houston, Texas, by Dr. De Bakey's group, showing that there is no active bacterial factor responsible for the irreversible phase of hemorrhagic shock. This does not apply to any endotoxin or endoprotein factor in the causation or nature of irreversible shock.

Prophylactic Postoperative Antibiotics

A Controlled Study of 1,007 Cases

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The value of postoperative prophylactic antibiotics in general surgery has long been debated. At the time this study was undertaken, sufficient evidence to condemn or justify such use of antibiotics had not been presented. In a complete review of the literature, several studies concerning this problem were found. McKittrick and, more recently, Sanchez-Ubeda published work suggesting that prophylactic postoperative antibiotics do not diminish the incidence of postoperative infections in general surgical patients. Appleton and Wisebrun in urology and Tachdjian and Compere in orthopedics reached similar conclusions. The present investigation studied the effect of routinely administered antibiotics on the postoperative course of general surgical patients. To assure the validity of the findings, it was necessary to meet two criteria. The first was that the number of patients be significantly large. The second was that the study be adequately controlled.

Materials and Methods

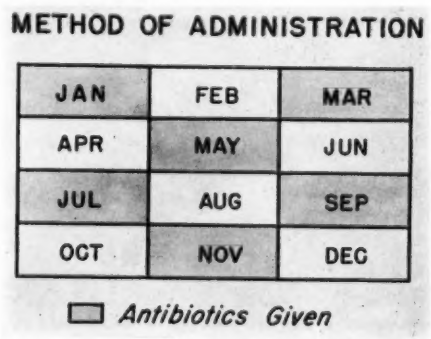
All major operative cases of the general surgical service in which adequate follow-up of the patient could be anticipated were considered potential candidates for the study. Emergency surgical procedures were excluded.

To assure standardization for valid sampling, the following criteria were established for exclusion from the series:

1. Concomitant infectious processes, related or unrelated to the surgical procedure contemplated.
2. Gross contamination of the operative site at the time of surgery. Surgical procedures about the mouth were considered contaminated.
3. Diabetes, neutropenia, steroid therapy, and other factors predisposing the patient to infection.
4. Administration of systemic antibiotics within a week prior to surgery.
5. Allergy to antibiotics.

For a 12-month period, the daily operating schedule was carefully reviewed the evening prior to surgery. The names of potentially eligible cases were entered on a chart posted in the recovery room. After the surgical procedure the responsible house officer determined the eligibility of the patient by the above criteria of exclusion. If, in the opinion of the house officer, the patient was ineligible for the study, the reason was noted on the recovery room chart, and the patient was dropped from the study. Eligible patients were designated by an appropriate mark next to the patient's name on the recovery room chart. The words "antibiotic study" were then entered in the patient's hospital order sheet. The recovery room nurse administered the antibiotic by intramuscular injection, and noted this on the patient's hospital record. On alternate months an identical procedure was followed except that the antibiotic was withheld (Fig. 1). At no time was the house officer informed of whether the patient was to be in the control or the experimental group. No antibiotics

Fig. 1.—Shaded blocks indicate the months in which antibiotics were given. On the alternate months antibiotics were not given.



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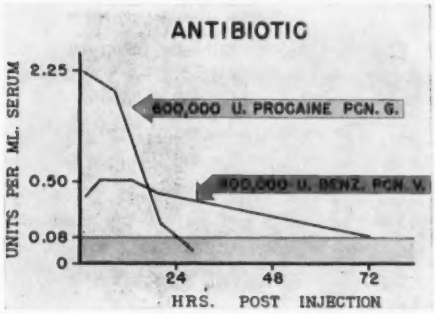


Fig. 2.—Therapeutic serum levels of penicillin. A comparison of benzathine penicillin V and procaine penicillin G. Serum levels above 0.08 units per milliliter are considered therapeutic.

were to be administered without adequate reason in the postoperative period.

An antibiotic or combination of antibiotics was sought which would be long acting, well standardized, easily administered with a single injection, and well tolerated. The product which most nearly met these requirements appeared to be a combination of long-acting benzathine penicillin V and dihydrostreptomycin in concentrations of 600,000 units and 0.5 gm. respectively. The release of the penicillin was such that therapeutic levels were maintained for 72 hours (Fig. 2). The streptomycin was almost completely dissipated within 24 hours. This combination of antibiotics was available to the patient without cost.*

After discharge, the charts of all the patients were carefully reviewed, and the relevant data were tabulated on electronic sorting cards. At the time of this evaluation, cases were eliminated if the follow-up was inadequate, or if antibiotics had been administered without reason. In the case of infectious complications, a record was kept of the bacteriology, the specific antibiotic sensitivity, the therapy instituted, and the course of the patient.

During the 12-month period covered by the present investigation, there were 2,987 procedures on the general surgical service. Of this number, 1,007 cases, or 33.7%, were included in this study; 1,980 cases were eliminated because of reasons previously stated.

Results

The nearly equal distribution of types of procedures between the control and experimental groups indicates the validity of the sampling method used (Table 1). There was no association of a specific operative procedure with any single type of infectious organism.

The 1,007 cases in this study were almost equally divided into the groups with and without prophylactic antibiotic administration. Antibiotics were given to 45%, and 55% received no antibiotics. The infectious complication rate of the 558 cases without antibiotics was 9.8%. There were 449 cases in the group given prophylactic antibiotics. The infectious complication rate was 11.4%. Most of these were wound infections (Table 2).

* Wyeth Laboratories furnished the drug combination used in this study.

TABLE 1.—*Distribution of Operations Between Control and Experimental Groups*

Procedure	No. of Cases	
	With Antibiotics	Without Antibiotics
Gastrectomy	27	37
Colectomy	18	14
Splenectomy	15	19
Thyroidectomy	37	51
Cholecystectomy	53	72
Total hysterectomy	7	6
Radical and simple mastectomy	23	20
Sympathectomy	6	7
Hemorrhoidectomy	22	37
Excision of tumor	37	51
Vein ligation and stripping	25	31
Inguinal hernia	79	88
Breast biopsy without mastectomy	20	51
Other miscellaneous	78	69
Totals	449	558

TABLE 2.—*A Breakdown of All of the Infectious Complications* *

Type of Complication	No. of Complications	
	With Antibiotics	Without Antibiotics
Wound infection	12	5
Dehiscence	4	0
Stitch abscess	3	2
Peritonitis	4	0
Intra-abdominal and subphrenic abscess	5	6
Draining sinus and infection	2	0
Urinary infection and cystitis	7	9
Atelectasis	8	6
Pneumonitis	7	5
Temp. elevation to 101.5 F without other reason	18	11
Totals	70	44

* In several instances there is more than one complication per case. The infectious complication rate has been based on the number of cases with infectious complications.

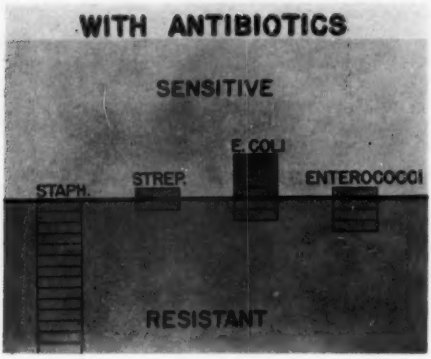
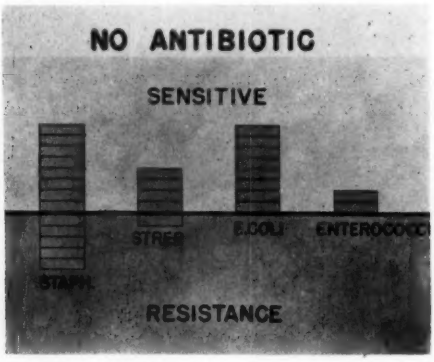


Fig. 3.—Comparison of resistant and sensitive bacteria in the control group. Each block represents an organism cultured from a single infection.

Bacteriology

An attempt was made to isolate and identify the responsible agent in every infection. The antibiotic sensitivity was determined whenever possible. There was a preponderance of the Gram-positive cocci infection both in the control and the experimental groups. In the group which was given antibiotics, 76% of the bacteria cultured from the infections were resistant to the antibiotics under study (Fig. 3). On the other hand, most of these infections responded favorably to other antibiotics and to surgical principles of therapy. In the control group only 22% of the bacteria responsible for the infections were resistant to either penicillin or dihydrostreptomycin (Fig. 4).

Fig. 4.—Comparison of resistant and sensitive bacteria in the experimental group. Each block represents an organism cultured from a single infection.



Conclusions

1. Prophylactic antibiotics as used in this investigation do not diminish the incidence of postoperative infection.

2. The administration of prophylactic antibiotics does predispose to the emergence of resistant strains of bacteria.

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Pseudomembranous Enterocolitis

The Experimental Induction of the Disease with Staphylococcus Aureus and Its Enterotoxin

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The objection to Staphylococcus var. aureus (Micrococcus pyogenes) as the etiologic agent of pseudomembranous enteritis stems from the observation that Staphylococcus has not been isolated in every case of the disease and from the assumption that the physical changes observed in the intestine are secondary to the associated shock. These objections are without foundation. S. aureus does not grow out on every culture medium. In a mixed flora it fails to grow out at all, unless the culture medium favors its growth and suppresses the competing micro-organism. Referring physicians have told me repeatedly that the stool cultures of their patients, desperately sick with pseudomembranous enterocolitis, did not grow out staphylococci. Upon culturing the stools of these patients on proper media the staphylococci grew out in dominant proportions. The oral administration of staphylococci to monkeys, animals highly sensitive to the enterotoxin, does not make them sick and does not induce stools positive for the micro-organism.[1] The Staphylococcus is destroyed in the intestinal tract as long as the intestinal tract is occupied by normal colonic flora. Furthermore, pseudomembranous enterocolitis is not always a fatal disease. In fact, it may be a transient manifestation of enterotoxin poisoning, similar to food poisoning. In such an event, a culture of the stool taken at the termination of the disease may not contain any staphylococci; they have been overgrown by the returning normal colonic flora. The abating symptoms of enteritis are due to the residuum of enterotoxin elaborated in vivo by the disappearing staphylococci. All these facts have been known in microbiology for a long time. The disregard of these important fundamental factors should not be considered as a threat to the security of Staphylococcus as the etiologic agent of pseudomembranous enterocolitis. The confusions are further multiplied when chronic lingering diarrheas or diarrheas caused by fungus infestations of the intestines are erroneously spoken of as pseudomembranous enterocolitis.

Identifying the changes observed in the intestine in an irreversible shock as a form of pseudomembranous enterocolitis is a misconception of even a greater magnitude. It has been stated that in an irreversible shock, such as one produced by a transfusion of incompatible blood, intravascular clotting occurs which gives rise to enteritis, identical with pseudomembranous enterocolitis.[2] Such a phenomenon, indeed, is totally unrelated to enterotoxin enteritis. In an irreversible shock the changes observed in the bowel mucosa are due to venous pooling and subsequent intravascular clotting of blood. These changes can be produced by any substance which suddenly and precipitously lowers the blood pressure to an irreversible state. These changes are immediate; they can be observed in the bowel mucosa in the very train of their development as the blood pressure becomes suddenly imperceptible. These many confusions and the fact that pseudomembranous enterocolitis persists as a serious and often fatal com-

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plication of major surgical procedures made it imperative to devise crucial experiments to correct such existing misconceptions.

In the general scheme of the experiments serious consideration was given to the selection of suitable experimental animals. It was noted that chinchillas develop fatal pseudomembranous enterocolitis spontaneously when tetracycline (Achromycin) pellets are included in their daily diets.[3] The disease develops after several months of antibiotic feeding and strikes about 5% of the animals. Since the usual laboratory animals, particularly dogs, are very resistant to S. aureus and totally insensitive to its enterotoxin, the chinchilla was selected as the main experimental animal. Cats and kittens, although resistant to Staphylococcus, react violently to its enterotoxin. These animals were therefore added to the experimental group. The chinchillas were used principally for the oral administration of staphylococcal suspension. Their intestinal tracts, after being disturbed by an oral administration of an antibiotic mixture, supported the growth of staphylococci and induced a fatal enteritis. The cats and kittens, whose intestinal tracts are resistant to staphylococci, received only the enterotoxin prepared from colonies grown on culture media.

The various strains of staphylococci used were isolated from stools of patients seriously ill with pseudomembranous enterocolitis or from food definitely implicated in human food poisoning. In all instances the staphylococci were isolated in pure cultures and tested for enterotoxin by the kitten or monkey tests.[4] This is a simple test used in microbiology in assaying enterotoxin. If enterotoxin is present, 2 to 5 ml. of the extract, introduced orally, will make a monkey or a kitten violently sick with retching and diarrhea. Every strain of staphylococci used was capable of elaborating potent enterotoxin in vitro. Since the enterotoxin-elaborating ability of the Staphylococcus played an important part in the experimental assumption, and since the presence of enterotoxin was known in every strain, the additional identification of the Staphylococcus by coagulase test became secondary and was not tested for.

The enterotoxin was extracted from vigorous cultures of staphylococci by the method of Woolpert and Dack.[5] In most instances the cultures represented pure isolates from stools of patients seriously ill with pseudomembranous enterocolitis. In another instance the enterotoxin was extracted from a culture of staphylococci isolated from frozen shrimps known to be implicated in food poisoning. This particular strain of Staphylococcus was extensively studied in the Microbiology Laboratories of The University of Chicago and, for the purpose of identification, labeled "S-6." This strain was particularly attractive because it persistently elaborated enterotoxin, and a specific test, the gel-diffusion precipitin test of Oudin,[6] had been developed for the detection of this enterotoxin.

The primary isolation of Staphylococcus demands a culture medium with strict nutritive requirements. The time-tested blood agar medium is satisfactory and was used most frequently. Occasionally, the primary isolates were obtained on the P-E medium of Brewer and Lilley (phenylethyl alcohol medium). In stools suspected of mixed microbial content, the highly selective tellurite-glycine medium of Zebovitz, Evans, and Niven Jr. was employed.[7]

With this experimental armamentarium and with a profound desire to apply and to adhere to principles long known and utilized in microbiology, two main sets of experiments were designed which fulfilled the four postulates of Koch.

Twelve chinchillas were used in the first set of experiments. They were from six to ten months old and weighed 300 to 375 gm. each. They were placed in separate cages and given their standard diet of cabbage, lettuce, and carrots. Eight chinchillas were experimented upon and four remained as controls. The eight experimental chinchillas received daily an oral

administration of an antibiotic mixture consisting of 12.5 mg. of chlortetracycline (Aureomycin), 12.5 mg. of oxytetracycline, and 25 mg. of sulfisoxazole (Gantrisin). This mixture was found, by sensitivity tests, to be most effective against the microorganisms existing in the normal stools of these chinchillas. Three chinchillas were given the antibiotic mixture for 18 to 21 days. Two milliliters of fresh saline suspension of pure staphylococci, isolated from a virulent case of pseudomembranous enterocolitis, were added as daily oral administration on the sixth day. From the sixth day on, these chinchillas received the antibiotic mixture in the morning and the staphylococcal suspension in the afternoon. They became violently sick 24 hours after the first administration of the staphylococci. They all exhibited lethargy, anorexia, and diarrhea. Death occurred on the 12th to 18th day following the first dose of staphylococcal suspension.

In two chinchillas the administration of the antibiotic mixture was terminated on the sixth day. From that day on, they received only the suspension of staphylococci. They promptly developed lethargy, anorexia, and diarrhea and died on the fifth and seventh day respectively.

Three additional chinchillas received the antibiotic mixture for five days; the staphylococcal suspension was initiated 24 hours later. The animals developed the usual symptoms of enteritis, but within four days returned to a state of vigorous health in spite of continual administration of the staphylococcal suspension. The staphylococcal feeding was continued over a period of 16 days, and then it became obvious that no effective change was being induced in them. The experiment was, therefore, terminated and the animals rested for 10 days. The same antibiotic mixture was readministered orally after the rest period. The chinchillas became sick with anorexia, lethargy, and diarrhea and died on the third and fourth day respectively. It must be remembered that the chinchillas did not receive the staphylococcal suspension in the second round of the experiment. It was feared, therefore, that the antibiotic alone induced the symptoms and death of the animals. This assumption was wholly incorrect because at necropsy the intestinal tracts of these chinchillas contained pure cultures of staphylococci. Death, therefore, was due to staphylococcal enterocolitis. In the first round of the experiment, 24 hours elapsed between the last dose of the antibiotic and the first dose of the staphylococcal suspension. A sufficient recovery of the normal colonic flora probably occurred during this lapse, preventing the staphylococci from establishing themselves in pathogenic proportions within the intestines of these animals. When the antibiotic mixture was readministered in the second round, a small, residual nidus of staphylococci within the intestine must have been able to grow into dominant colonies. Nevertheless, this observation made an obvious and previously conceived control even more imperative. A control experiment was set up to test the effect of the antibiotic given alone.

Three normal chinchillas were given the usual antibiotic mixture daily for 10 days. They were observed for one month, and during this period they remained in vigorous health. Frequent cultures of their stools failed to grow out staphylococci. A fourth chinchilla received no medication at all and was killed to obtain gross and microscopic specimens of normal gastrointestinal tract.

The experiments thus far conducted are summarized in Tables 1 and 2.

At necropsy all experimental chinchillas showed severe gastroenterocolitis. The appearance of the gastrointestinal tract of normal controls differed strikingly from that of the experimental animals (Figs. 1 and 2). The entire tract was distended and edematous. The segmented, hard stool seen in the colons of control animals was replaced by mushy, diarrheal stools. The small bowel, in particular, exhibited hemorrhagic changes in the mucosa.

TABLE 1.—*Eight Chinchillas Given Orally 12.5 Mg. Chlortetracycline, 12.5 Mg. Oxytetracycline and 25 Mg. Gantrisin Daily and Subsequently Given a Suspension of Staphylococcus Aureus Developed Fatal Enterocolitis*

No. of Chinchillas Used	Antibiotics, No. of Days Given	Staph. Began on Day No.	Death Occurred on Day No.	Necropsy	Staph. Reisolated
3					
Nos. 1, 2, 3	19, 18, 21	6, 6, 6	13, 12, 18	Enteritis	In pure culture
2					
Nos. 4, 5	6, 6	6, 6	5, 7	Enteritis	In pure culture
3					
Nos. 7, 8, 9	5, 5, 5	6, 6, 6	Survived	—	—
3					
Nos. 7, 8, 9	4, 3, 4	0, 0, 0	4, 3, 4	Enteritis	In pure culture

TABLE 2.—*The Oral Administration of an Antibiotic Mixture to Normal Chinchillas Does Not Induce Enteritis*

No. of Chinchillas Used	Antibiotics, No. of Days Given	Results
3		
Nos. 10, 11, 12	10, 10, 10	No effect
1		
No. 6	None	No effect

Microscopic views of the duodenum revealed severe destruction of the mucosa, ulcerations, and a fibrinomucous pseudomembrane. A comparison with a normal section of the duodenum is shown in Figure 3. The destructive enteritis was perhaps even severer in the jejunum. The microscopic section compared with a section of normal jejunum, illustrated in Figure 4, shows almost a total destruction of the mucosa and a lumen filled with a fibrinomucous exudate. A high magnification of a section of duodenum reveals a replacement of the mucosa by leukocytic infiltrate extending into the muscularis, marked edema, and a general breakdown of all the layers except the serosa (Fig. 5).

These spectacular findings here illustrated do not, by any means, represent postmortem autolytic changes which they re-

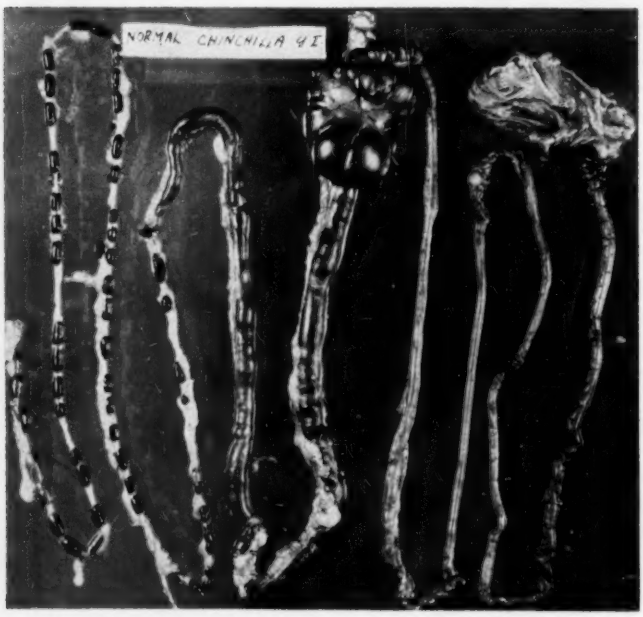

Fig. 1.—Gastrointestinal tract of a normal chinchilla. Note the segmented stool in the colon. The magnification is slightly higher than in Figure 2.

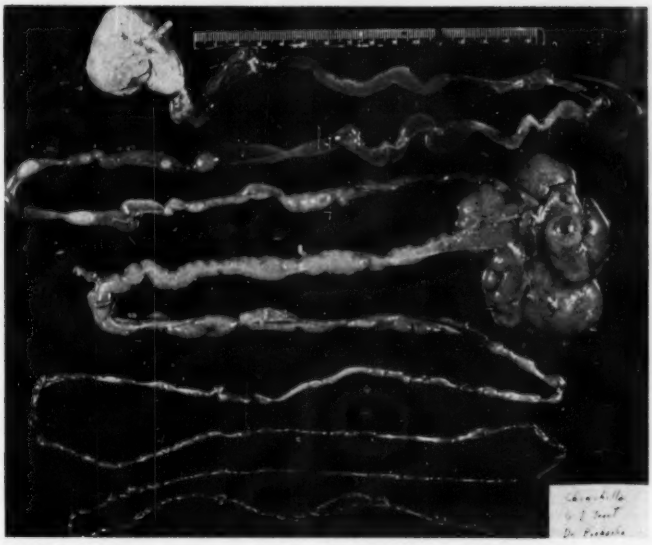

Fig. 2. — Gastrointestinal tract of a chinchilla killed when near death from enteritis. Note the greatly distended cecum and the absence of segmented stool in the colon.

semble. Most of the chinchillas were observed in their final moments of life and autopsied within minutes after their deaths. The microscopic sections were checked against corresponding sections obtained from normal chinchillas whose bodies were kept in the icebox for 18 hours after death. These control sections showed no demonstrable autolytic changes.

Cultures of the intestinal tract, taken at necropsy, revealed pure isolates of S. aureus in all experimental chinchillas. The reisolated staphylococci again elaborated enterotoxin, which gave a strongly positive reaction in the kitten or monkey. The cultures of all control animals showed only the usual, normal colonic flora.

Implicating the Staphylococcus as the agent of experimentally induced enteritis might have been the final goal in the search for the etiology of pseudomembranous enterocolitis, had it not been for the fact that

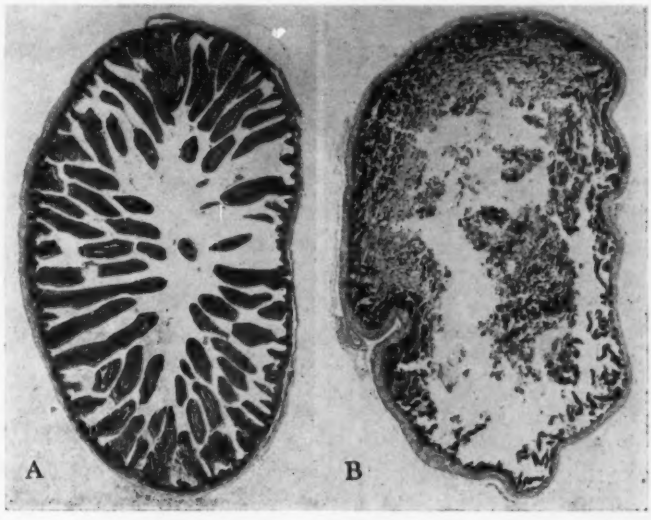

Fig. 3.—Section *A* is through the duodenum of a normal chinchilla. Section *B* is from a corresponding level of duodenum of a chinchilla with severe enterocolitis. Note the destruction of the mucosa and the fibrinomucous pseudomembrane.

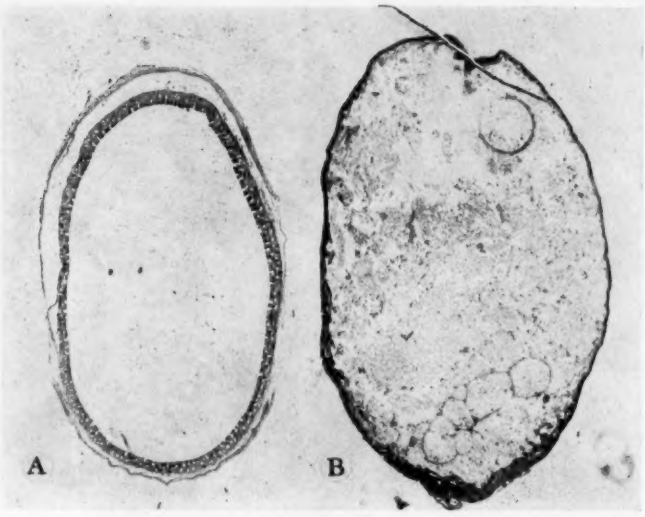

Fig. 4.—Section *A* shows normal jejunum. Section *B* is a jejunum of a chinchilla with severe enterocolitis. Note the distension, the complete destruction of the mucosa and the fibrinomucous exudate in the lumen.

staphylococci elaborate enterotoxin. It became mandatory to devise experiments for testing the effect of the enterotoxin on susceptible animals. Cats and kittens were known to be sensitive to the enterotoxin and therefore were selected for the experiment. It had been established in previous experiments that antibiotic-treated chinchillas were able to grow staphylococci in their intestines. If the symptoms of the enteritis and the death of the animals were due to the enterotoxin elaborated in vivo, then the same events should be reproducible in normal animals by the oral administration of the enterotoxin prepared in vitro. Thus, chinchillas had to be included in the enterotoxin experiments.

Six normal cats received daily or twice daily 10 ml. of fresh enterotoxin by mouth for a period of 12 to 34 days. They all developed symptoms of enteritis marked by lethargy, anorexia, and diarrhea. They were killed on the 12th to 34th day. At necropsy all the cats showed gross evidence of enteritis, usually limited to the proximal jejunum (Fig. 6). The microscopic sections

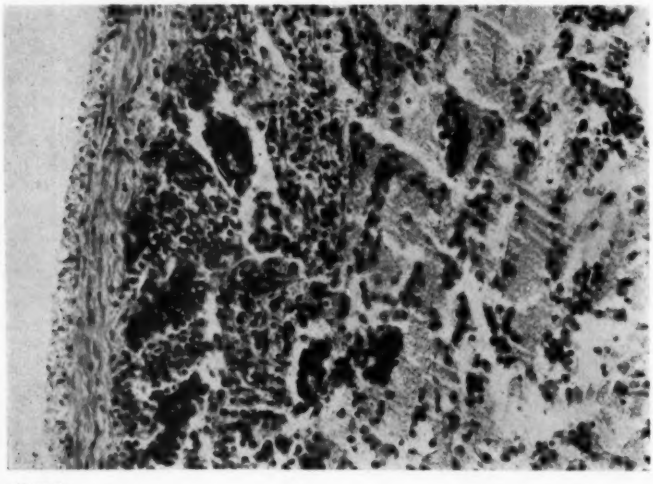

Fig. 5.—A high-power magnification of a section through the duodenum. This chinchilla died from induced staphylococcal enteritis. Note the replacement of the mucosa with leukocytic infiltrate, edema, and mucinous exudate.

through the involved jejunum showed, in each instance, a marked leukocytic infiltration and denudation of the mucosa, with sloughing of the villi, erosions of the muscularis, and submucosal edema (Fig. 7). Periodic cultures of the stools showed no evidence of staphylococci at any time. The enteritis was induced entirely by the enterotoxin.

In the second assignment of the experiment seven kittens were given a daily dose of 10 ml. of enterotoxin orally for 12 to 23 days. Their symptoms of enteritis, as well as the gross and microscopic findings at necropsy, were found to be severer than those observed in the cats. An illustration

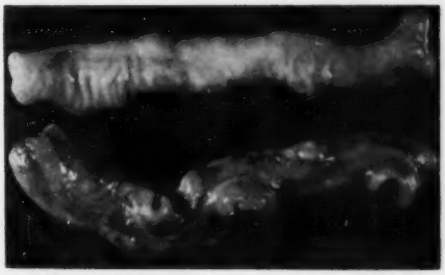

Fig. 6.—The two segments represent distal and proximal jejunum of the same kitten. The thinner, distal segment is normal; the thicker, proximal segment shows jejunitis.

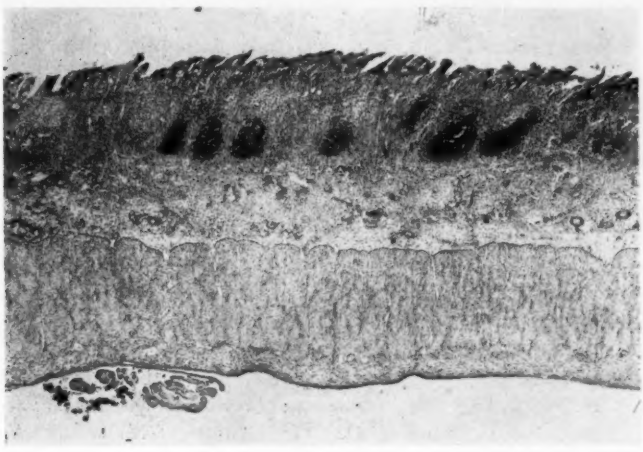

Fig. 7.—A segment of the jejunum of a cat shows moderately severe jejunitis following an oral administration of staphylococcal enterotoxin. Note the disruption of the villi, mucosal erosions, and submucosal edema.

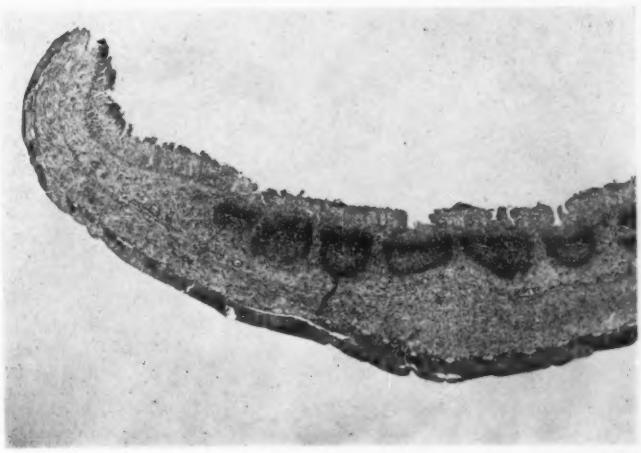

Fig. 8.—A severe jejunitis in a kitten induced by oral administration of enterotoxin. Note the frank ulcerations and the denudation of the mucosa.

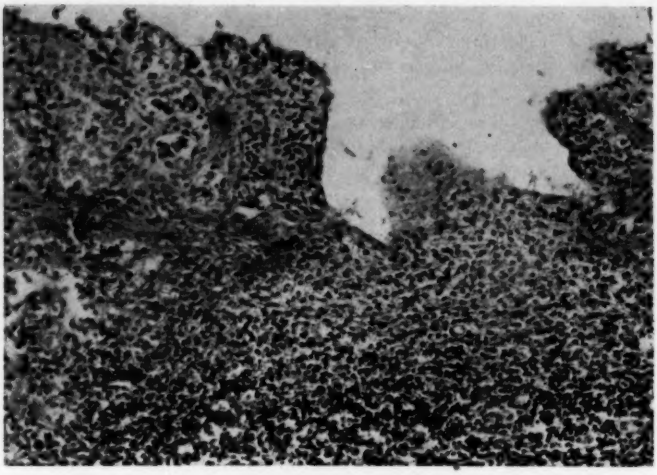

Fig. 9.—A high-power magnification of severe jejunitis produced in a kitten with enterotoxin. Note the heavy leukocytic infiltration, the loss of mucosa, and the minute ulcer.

of a severe ulcerative jejunitis is presented in Figures 8 and 9.

In the terminal phase of the experiment four chinchillas were placed on a daily oral intake of 4 ml. of enterotoxin until death occurred in 3 to 12 days. Within a few hours after the administration of the first dose of enterotoxin, the chinchillas developed severe diarrhea, lethargy, and tenesmus. With each subsequent daily dose they became weaker and they died in a convulsive state. At necropsy the gross findings were identical with those found in the antibiotic-treated chinchillas receiving the staphylococcal suspension. The entire gastrointestinal tract was distended and edematous. The small bowel showed hemorrhagic mucosa. The normal segmentations in the colon were absent and the lumen filled with watery stool. The microscopic section of the stomach, duodenum, jejunum, and the colon showed destruction of the mucosa, submucosal edema, deep ulcerations, and fibrinomucous pseudomembrane. A typical section, that of the duodenum, is illustrated in Figure 10. The high magnification illustrated in Figure 11 by a section through the colon shows heavy leukocytic infiltration,

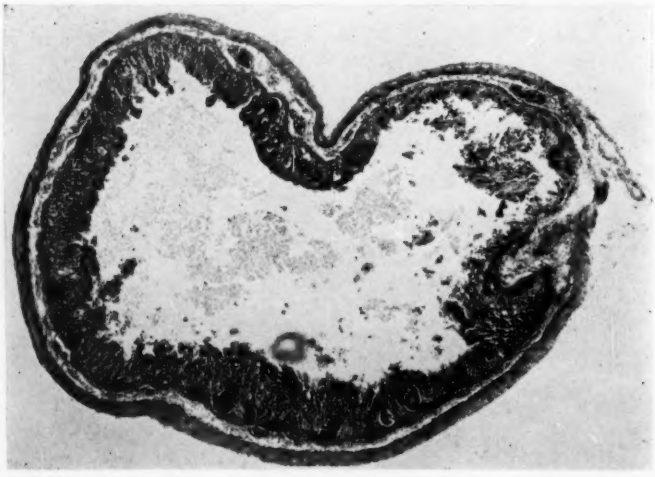

Fig. 10.—A section through the duodenum of a chinchilla receiving enterotoxin for four days. Note the severe ulcerations, destruction of the mucosa, and the membranous exudate in the lumen.

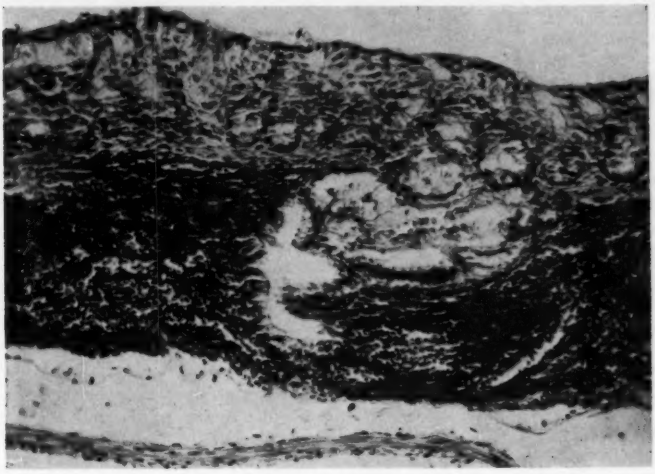

Fig. 11.—A section through the colon of a chinchilla fed with enterotoxin shows heavy leukocytic infiltration, denudation of the mucosa, and a complete loss of the glandular structures.

TABLE 3.—*Susceptible Animals Develop Nonfatal or Fatal Enteritis upon Oral Administration of Staphylococcal Enterotoxin*

	No. of Days 10 Ml. Enterotoxin Given; Day of Killing or Death	Symptoms	Necropsy
6 Cats			
Cat no.	1, 2, 3, 4, 5, 6	Lethargy	Enteritis
No. of days	12 19 33 14 34 13	Anorexia Diarrhea	
7 Kittens			
Kitten no.	10, 11, 12, 13, 14, 15, 16	Lethargy	Enteritis
No. of days	18 18 23 12 12 18 19	Anorexia Diarrhea	
4 Chinchillas	4 Ml. of Enterotoxin		
Chinchilla no.	23, 24, 25, 26	Lethargy	Enteritis
No. of days	3 4 5 12	Anorexia Diarrhea Death	

denudation of the mucosa with a complete loss of the glandular structures. These experiments are summarized in Table 3.

It is important to realize that the cats, kittens, and the last group of chinchillas never received any antibiotics. The enterotoxin given them was extracted from pure cultures of staphylococci isolated from cases of pseudomembranous enterocolitis or, in one instance, from spoiled food implicated in human food poisoning. Furthermore, the stool cultures of these animals remained normal, and at necropsy no staphylococci could be isolated. Lastly, the enterotoxin used was fresh and repeatedly cultured for the presence of staphylococci. Most of the cultures remained sterile, and only an isolated colony of staphylococci was occasionally found. Since no staphylococci were detected in the stools of the animals, it is reasonable to assume that the occasional Staphylococcus introduced with the enterotoxin was destroyed in the presence of normal intestinal flora. The absence of staphylococci in the intestinal tract of the experimental animals receiving only the enterotoxin indicates conclusively that the enteritis is produced by the enterotoxin alone.

Conclusions

1. Fatal enterocolitis is induced in antibiotic-treated chinchillas by the oral administration of particular strains of staphylococci.

2. Fatal enterocolitis is induced in normal chinchillas by the oral administration of staphylococcal enterotoxin.

3. Nonfatal enteritis is induced in normal cats and kittens by the oral administration of staphylococcal enterotoxin.

4. Pseudomembranous enterocolitis develops in man when colonies of staphylococci are able to grow in his intestine and elaborate enterotoxin.

5. The symptoms of pseudomembranous enterocolitis, the physical changes observed

in the bowel, and the fatal termination of the disease are due to the enterotoxin.

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Potential Dangers Associated with Antibiotic Administration During Anesthesia and Surgery

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Antibiotic administration during surgery may be associated with hazards not normally encountered in unanesthetized subjects. We submit this contention on the bases of recent evidences in the literature and our laboratory investigations stimulated by clinical experiences. The potential dangers are not those usually associated with prolonged or repeated administration of these drugs, such as allergic responses, blood dyscrasias, nephro- and ototoxic phenomena, but rather acute states of respiratory or circulatory depression.

A drug may be therapeutic under usual circumstances of administration and toxic when altered conditions prevail. The patient during surgery is indeed different from an unanesthetized subject. A number of factors could conceivably affect his response to a drug. Anesthesia poses the possibility of drug interaction with a variety of agents used for that purpose. Changes in concentrations of circulating hormones in response to surgical stress and anesthesia may modify the effect of exogenous agents. Hemodynamic changes such as decreased blood volume and hypotension may intensify the action of depressants. Absorption, distribution, and elimination of drugs may be influenced by hemodynamic changes or the direct pharmacologic effect of anesthetic agents upon organ systems and metabolic functions. Ionic shifts resulting from tissue trauma, fluid loss and replacement, and disturbances of respiratory functions may modify drug effects. Finally, the patient during surgery may present routes of drug administration, such as arterial or intraperitoneal, not commonly employed. The rapid absorption associated with intraperitoneal administration and interactions of absorbed drug with other agents appear particularly relevant to acute manifestations of toxic responses to antibiotics.

There have been reported [1-7] a number of instances of severe respiratory depression following the intraperitoneal administration of neomycin sulfate during surgery. Most of these toxic responses occurred during ether anesthesia. Some deaths have resulted; however, most cases survived after protracted care involving artificial ventilation. Respiratory depression associated with neomycin sulfate administration during surgery and the reported ineffectiveness of analeptic agents [4,6] including pentylenetetrazol (Metrazol), pictrotoxin, nikethamide (Coramine), lobeline, and carbon dioxide suggested a peripheral rather than a central depressant action of the antibiotic.

The mechanism of action responsible for this toxic phenomenon has been elucidated.[7,8] Neomycin sulfate is a neuromuscular blocking agent similar in action to ether and *d*-tubocurarine chloride. Potentiation of this pharmacologic action of the antibiotic has been observed in the laboratory when used in combination with ether or *d*-tubocurarine chloride. In the dog respiratory depression parallels the neuromuscular blocking action of neomycin sulfate. Neostigmine methylsulfate (Prostigmine) has been demonstrated to be an effective antagonist of the respira-

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tory and neuromuscular depressant actions of neomycin sulfate. Clinical application of this observation has been reported.[5]

The neuromuscular blocking action of streptomycin sulfate has also been reported[9] and the observation confirmed in our laboratory. In addition, neuromuscular blocking actions of dihydrostreptomycin sulfate, polymyxin B sulfate, and kanamycin sulfate have been demonstrated in unanesthetized rabbits following intravenous administration of these drugs in doses of 100 mg/kg. These doses admittedly exceed those commonly employed clinically, but, if the neuromuscular blocking action of these drugs were enhanced like that of neomycin sulfate, similar clinical results might occur.

We have recently observed another interesting response associated with the administration of an antibiotic during surgery. Near the end of an abdominal perineal resection conducted with nitrous oxide anesthesia and adjunctive agents including *d*-tubocurarine chloride, there occurred a precipitous hypotension associated with the intraperitoneal administration of 1 gm. of streptomycin sulfate. Systolic pressure declined from 140 mm. of Hg to 80 mm. of Hg, then rebounded to the hypertensive level of 220 mm. of Hg. This observation of hypotension and others noted in animals focused our attention upon this potentiality of antibiotics. Slow intravenous infusions of streptomycin sulfate in rabbits produced a progressive hypotension. Associated hypoventilation increased the hypotensive effect, which could be alleviated to some degree by artificial ventilation. The hypertensive rebound observed in the human being has not been seen in the laboratory.

Eleven antibiotic agents administered intravenously to rabbits were evaluated qualitatively for their neuromuscular blocking and hypotensive actions. Neomycin sulfate, dihydrostreptomycin sulfate, streptomycin sulfate, polymyxin B sulfate, and kanamycin sulfate exhibited both actions. Neostigmine methylsulfate was effective in antagonizing the neuromuscular blocking action of neomycin sulfate, dihydrostreptomycin sulfate, and streptomycin sulfate, but tended to enhance this action of polymyxin B sulfate and kanamycin sulfate. Erthromycin lactobionate, tetracycline hydrochloride, bacitracin, and oleandomycin did not produce neuromuscular blockade but were active hypotensive agents. The hypotensive action of all drugs was more pronounced following rapid intravenous administration than with slow infusion. Potassium penicillin G and ristocetin were inactive in both regards. Doses of bacitracin and potassium penicillin G were 20,000 units/kg. and 200,000 units/kg. respectively; all other antibiotics were tested using doses up to 100 mg/kg.

Comment

We are unaware of any clinical reports of respiratory depression or hypotension involving the use of antibiotics other than neomycin sulfate and streptomycin sulfate. It is hoped that awareness of inherent pharmacologic effects of these agents may help to prevent further instances of clinical difficulty. Avoidance of overdosage, excessive absorption, and drug interactions should be helpful in this regard. When intraperitoneal antibiotics seem indicated, the possibility of undesirable drug interactions may be minimized by postoperative administration through catheters placed during surgery. This technique of administration has been described.[10]

The following clinical questions are suggested for considerations based upon available pharmacologic information. What may be the effect of high systemic levels of certain antibiotics resulting from their administration prior to anesthesia and surgery? Are inflammatory states of bowel and peritoneum likely to contribute toward systemic absorption of antibiotics? Might spillage of residual preparatory antibiotics from the bowel during surgery lead to rapid intraperitoneal absorption? Would the neuromuscular blocking action of some antibiotics aggravate the state of a person afflicted with myasthenia gravis?

Symptomatic treatment is indicated for respiratory or circulatory depression result-

ing from the administration of antibiotic agents. Such treatment includes maintenance of airway patency, artificial ventilation with oxygen, and the use of vasopressor agents if indicated. Neostigmine methylsulfate may be a useful adjunct in treating respiratory depression caused by neomycin sulfate, dihydrostreptomycin sulfate, and streptomycin sulfate. Laboratory evidence suggests that neostigmine methylsulfate may enhance, rather than antagonize, respiratory depression produced by polymyxin B sulfate and kanamycin sulfate.

Summary

This paper discusses clinical and laboratory evidences of neuromuscular blocking and hypotensive actions of various antibiotic agents. Dosage, rate of absorption, drug interactions, and clinical circumstances appear to be major determinants in the development of complications arising from antibiotic administration during anesthesia and surgery. Suggestions for treatment have been provided.

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DISCUSSION

ON PAPERS BY DRS. BARNES, PACE, TRUMP, AND ELLISON; BY DR. PROHASKA, AND BY DRS. PITTINGER AND LONG

DR. WILLIAM E. ABBOTT, Cleveland: I would like to make a few comments concerning Dr. Pittinger's very interesting and timely presentation. Dr. William E. Schatten and I worked on the problem of treating bacterial peritonitis by the intraperitoneal instillation of broad-spectrum antibiotics about five years ago. Various antibiotics were screened, but because oxytetracycline (Terramycin) and subsequently neomycin had no local irritating effects these two agents were further investigated. An experimental appendiceal peritonitis was produced which caused death within two days in 100% of the 18 control dogs. In a second group of 17 animals an experimental peritonitis was produced in a similar manner; however, these dogs were given 400 mg. of oxytetracycline intravenously twice a day. All of the animals in this latter group died of peritonitis by 55.4 hours. In the third group of animals, peritonitis was produced comparable to that in the first two groups, but these dogs were given 400 mg. of oxytetracycline intraperitoneally twice a day for two days and intravenous fluids similar to that given to the first two groups. In this latter series there was a four-day mortality rate of 25%, and at the end of 21 days 52% of the animals had died. However, all of these animals were autopsied, and in no instance was peritonitis or septicemia present in the animals dying after the fourth day. Therefore, oxytetracycline given intraperitoneally was effective in combating peritonitis in 75% of the dogs treated by this technique while 100% of the control animals and the group of dogs who received oxytetracycline intravenously survived for 48 and 55.4 hours respectively.

Dr. Pulaski and his associates subsequently reported similar results in the treatment of experimental peritonitis and concluded that the intraperitoneal administration of an antibiotic was more effective in combating this disease than when the same intravenous antibiotic was given intravenously, intramuscularly, or orally. In another group of animals in whom peritonitis was produced, Dr. Schatten reported that 400 mg. of neomycin, given intraperitoneally twice a day, was at least as effective as the intraperitoneal ad-

ministration of oxytetracycline. In these animals, cultures of the peritoneal fluid taken six hours after the onset of treatment were all sterile, and again a very high survival rate was noted. Since that time we have treated over 100 patients by the intermittent instillation of either 250 mg. of oxytetracycline or 250 mg. of neomycin every six hours for two days and have noted no ill effects. In several instances these antibiotics were given to patients who were to undergo surgery, and after two days when a laparotomy was performed there was no evidence of any chemical irritation or adhesions.

It should also be emphasized that when sudden death has occurred following the intraperitoneal instillation of neomycin it has been in a deeply anesthetized patient and in most instances excessively large doses of neomycin were employed. We therefore believe that, while Dr. Pittinger has pointed out that neomycin has a toxic effect when it is rapidly absorbed in large quantities, the avoidance of deep ether anesthesia and muscle relaxants or the instillation of neomycin through a small plastic catheter postoperatively would be safe. During anesthesia oxytetracycline could be used and afterwards it would be safe to inject 250 mg. of either oxytetracycline or neomycin intraperitoneally every six hours. Since this has been proved to be an effective method of combating intraperitoneal infection, it does not seem logical to abandon it because some patients had been given excessive doses of neomycin. All difficulties should be avoided if the dose was limited to 250 mg. of neomycin in adults or if such treatment was started after the anesthetic has worn off.

Again, I would like to congratulate the author and encourage him to continue his studies, especially concerning the action of other antibiotics.

DR. ROBERT C. HICKEY, Iowa City: I think we as surgeons should be particularly grateful to Dr. Pittinger for this presentation. Forewarned as we are now, we are forearmed against intraperitoneal administration of these drugs or inadvertent intraperitoneal contamination.

At this meeting it might be pertinent to point out that Dr. Pittinger's data are international in scope. One instance which was afforded to him for study was supplied by a surgeon of Western Canada who sought consultation to explain an observed phenomenon following drug administration intraperitoneally of a broad-spectrum antibiotic that ended in death.

Dr. Pittinger, to sum up, has told us that these broad-spectrum antibiotics, these antimicrobial drugs, have pharmacologic activities of a profound nature. This is not at all surprising; as a matter of fact, it might be even somewhat hopeful. The very existence of the antibiotics is but a reflection that living systems are capable of synthesizing products beyond the ability of our laboratory chemists, and historically this has always been true. We use the antibiotics now to control infection, but perhaps we can harness these other properties for some type of independent use.

Especially I would call your attention to the possibility that in the antibiotics, the crude filtrates, and the sludge tanks, there may rest inhibitory substances which can control cellular systems, and perhaps by specifically harnessing these we may be able to develop a real tool to ameliorate or perhaps control or even eradicate some of our neoplastic diseases.

DR. HAROLD LAUFMAN, Chicago: I would like to express my gratitude to Dr. Prohaska for presenting his data on enteritis in the chinchilla. Two men in our laboratory, Drs. Menaker and Van Hagen, performed an experiment in a dog, similar to Dr. Prohaska's first experiment, and were able to produce a minimum lesion which had all the characteristics of enterocolitis except that the dogs did not go into shock. The dog is a nonsusceptible animal, but these were indicative experiments.

I sincerely hope that now that Dr. Prohaska has a lesion which is predictable and which is apparently so similar to the human type of disease he will now proceed and give us the answer to the $64 question, "How does one treat this disease?" I hope his future experiments will be directed to the therapeutic end.

DR. WILLIAM R. CULBERTSON, Cincinnati: I would like to express my appreciation to Dr. Barnes and his fellow workers for their paper, because they have given us very valuable objective data demonstrating one of the causes of the troubles that surgeons are having at present with infections occurring in their hospitals and in their operative cases.

Contributing to the development of this problem has been the use of certain improper antibiotics for both the treatment and the prophylaxis against infections. These antibiotics are the types which are compounded so that they are slowly absorbed, and result in the production of blood levels which are relatively low but still classified as therapeutic. The blood levels with these drugs, however, drop back to levels below therapeutic and remain so for several hours, sometimes even days. It is at this point that such modifications of the antibiotics tend to encourage the development of organisms resistant to the antibiotic. This is done by subjecting the bacteria present in the patient to subtherapeutic and sublethal quantities of the antibiotic for many hours.

The usual hospital-acquired staphylococcal infection is caused by strains of this organism which are resistant when exposed to the usual therapeutic levels of penicillin. They are, however, not

considered resistant in vitro when the levels are much higher, that is, in the neighborhood of 10 units/cc.

Dr. Barnes and his co-workers have used in their study streptomycin as one of the "prophylactic antibiotics." For the usual surgical infection this antibiotic is the least desirable for prolonged use. We have demonstrated that, after seven days of continued use, one-third of the common Gram-negative bacilli occurring in surgical infections developed resistance to streptomycin.

I agree with Dr. Barnes and his group in the conclusions concerning the prophylactic use of antibiotics in clean operative cases and feel that they have demonstrated in a concise and clear way the ineffectiveness of using antibiotics in this fashion.

Dr. H. S. Morton, Montreal: This trilogy of papers is most interesting and stimulating. I would like to ask Dr. Barnes one question.

In his prophylactive use of the antibiotics does he exclude preoperative bowel and stomach preparation in those cases that have no acidity? In our own experience we have found that the preoperative use of the sulfonamides, particularly the non-absorbable ones, and then one day only of neomycin, have been very valuable in the reduction of post-operative mortality, particularly from peritonitis, which has practically disappeared in the colonic cases, and to some extent in the stomach cases as well.

Dr. Pittinger's paper is very interesting, and I am most stimulated because it supports Dr. Altemeier's view that the antibiotics should not be used intraperitoneally. Some years ago it was fielder's choice; now it seems to be on a scientific basis.

However, in severe cases of peritonitis I still like to follow Dr. Abbott's recommendations and use 1 gm. of streptomycin and 1,000,000 units of penicillin intraperitoneally, not intravenously, as I think these have a lowering effect on the mortality in very acute cases, and you can leave a small catheter in place and repeat this dosage for four or five days.

Dr. Edward S. Judd, Rochester, Minn.: I congratulate Dr. Prohaska on having produced pseudomembranous disease in animals. Our laboratory had attempted this somewhat earlier, using the monkey, and had not been successful. His method, however, was somewhat different from ours.

I wish to ask Dr. Prohaska one question: Are you now seeing clinically in man any cases of pseudomembranous disease in which you cannot get positive cultures of the Staphylococcus in spite of the most modern of the media and the most modern of the inhibitors in the media?

Dr. William A. Altemeier, Cincinnati: I would like to make a very few remarks and ask a few questions.

First, to Dr. Barnes: Were there any beta hemolytic streptococcal infections that occurred in the wounds reported in your paper?

In a study in which I participated between 1942 and 1945, using first the sulfonamides, then penicillin, and then streptomycin with penicillin as prophylactic measures in contaminated wounds of violence, we found it was possibie to prevent pneumococcal and invasive streptococcal infections. We could not prevent staphylococcal infections, however, and to the best of my knowledge this is still true. Therefore, there is a limited place for prophylactic antibiotic therapy with penicillin in the recently injured patient to prevent invasive pneumococcal and hemolytic streptococcal infections.

I would like to ask Dr. Prohaska if he has phage-typed the Staphylococcus used in these experiments, and if all of his animals in which he produced the infection developed septicemia. I am particularly interested in whether or not there is a particular phage-type of Staphylococcus that is responsible for the disease of pseudomembranous enterocolitis.

Finally, I wish to state that I do not use and do not believe in the intraperitoneal instillation of antibiotic agents in the treatment of patients with peritonitis. I think it is unnecessary, and I believe it is fraught with some danger and the risk of complications. All of the broad-spectrum antibiotics have toxic effects under various conditions, and the number of papers that are appearing in the literature during the past three or four years are increasing rapidly.

Just to emphasize one point very briefly, we have a running series of penetrating wounds of the abdomen at the Cincinnati General Hospital, which has extended from January, 1942, to the present time. At first these patients were treated with sulfadiazine and sulfanilamide intraperitoneally and parenterally. The mortality rate was reduced from approximately 60% to 9%-11%. We then added penicillin to the sulfonamide therapy, and the mortality rate stayed between 9% and 11%.

Some of our enterprising residents then added streptomycin, giving three chemotherapeutic agents. The mortality rate stayed between 8% and 11%. At the present time, regardless of the antibiotics used, as long as penicillin is one of them the mortality rate has remained essentially unchanged.

Of particular interest is the fact that only three patients in this period of time have died with peritonitis, and in each instance the peritonitis was a

result of an overlooked perforation or a leaking anastomotic suture line.

DR. JAMES E. BARNES, Columbus, Ohio: I wish to thank Drs. Culbertson, Morton, and Altemeier for their comments on this work.

In answer to Dr. Morton, the oral nonabsorbable sulfonamides and neomycin are used routinely in the bowel cases included in the study. These cases were included, as were gastric resections.

We have two other slides that we might show.

[Slide] Dr. Culbertson mentioned the predisposition of staphylococci to become resistant to penicillin. In this slide we see the experimental group of those who received antibiotics. All of the staphylococci cultured from the infections in this group were resistant. In the case of streptococci there were two infections; one of these was resistant and the other was sensitive.

[Slide] In the control group, those who received no antibiotics, the resistance of the staphylococci was not as great. In this group the incidence of infection with streptococci was increased over the experimental group.

DR. JOHN VAN PROHASKA, Chicago: I would like to answer the questions first.

I am well acquainted with the experiment Dr. Laufman alluded to. It was done on dogs, and the animals were partially obstructed. I read the paper before it was published. I am sure that if we reinvestigate this particular experiment we will find the changes were due to partial obstruction of the bowel.

Dr. Judd, it would be most difficult to produce micrococcal enteritis in the monkey. The monkey is very sensitive to the enterotoxin; in fact, this reaction is used in the monkey test for enterotoxin. No matter what antibiotic we gave to our series of monkeys, we were unable to disturb sufficiently their normal colonic flora. Micrococcus pyogenes does not grow well in the presence of normal colonic micro-organisms. Enterotoxin introduced by mouth will produce moderate enteritis, usually confined to the jejunum.

I have observed several clinical cases in which there were no positive cultures for Staphylococcus. We cultured them on tellurite-glycine media, and usually obtained the positive cultures. Also, if the culture is taken at the termination of the disease, when the normal colonic micro-organisms are returning, the overgrowth of the coliforms on the plate may suppress the Staphylococci. It is an excellent question, for which obviously I do not have the full answer.

Dr. Altemeier, I did not classify the staphylococci. Most of them were coagulase-positive. We were mainly interested in their ability to elaborate enterotoxin, and all of the cultures we used were tested for enterotoxin. This work is in progress, as well as the work on other enterotoxins and endotoxins.

I have not tested the animals for septicemia.

DR. CHARLES B. PITTINGER, Iowa City: I would like to thank Dr. Hickey for discussing my paper, and I appreciate the comments of Drs. Abbott and Morton.

Dr. Abbott made two suggestions regarding the use of antibiotics and anesthesia. One was that the anesthetic regimen be altered, and the other that antibiotics be administered after anesthesia.

In regard to the first suggestion, the production of good relaxation is usually dependent upon neuromuscular blocking activity of muscle relaxants or that inherent in anesthetic agents themselves. Achievement of adequate relaxation without this pharmacologic effect may be difficult or impossible. The administration of antibiotics through catheters at a time when the effects of anesthetic agents and muscle relaxants have been dissipated seems more reasonable.

Effect of an Intravenous Fat Emulsion on Blood Coagulation

JOSEPH A. WERR, M.D., and FREDERICK W. PRESTON, M.D., Chicago

The use of intravenous emulsions has been limited by the high incidence of reactions associated with the injection of these substances into the blood stream. The reactions most frequently observed have occurred within a few minutes to several hours after beginning the infusions. The commonest of these is febrile in nature, often accompanied by a chill. More serious is the colloid reaction, thought to be caused by the introduction of colloids into the blood stream. Other toxic effects include anorexia, nausea, vomiting, headaches, dizziness, and vasomotor phenomena.

Early reactions of this type to an improved 15% cottonseed oil emulsion * have been of minor consequence. This has encouraged extensive clinical trials with this emulsion and has made possible its administration for many consecutive days. The low toxicity and metabolic effects of this emulsion are documented in recent published reports.[5,7,9,11,12,17]

Late reactions may occur in patients who have been given repeated infusions of fat emulsions. Watkins has described a serious illness characterized by hepatomegaly, fever, jaundice, and abnormal liver function in one patient on two occasions, once after 27 consecutive daily infusions of 600 ml. of Lipomul I. V. and again 60 days later after 26 consecutive daily infusions. Levenson, Upjohn, and Sheehy reported severe reactions in two patients given 1,200 ml. of Lipomul I. V. for 14 and 21 consecutive days, respectively. Lethargy, anorexia, nausea, vomiting, fever, bleeding into the gastrointestinal tract, and anemia occurred in both.

The maximum amount of intravenous fat that can be safely given has not been clearly defined. The amount given to the patients mentioned above totaled 15,600 ml. or more given over periods of 14 days or longer. This apparently was more than the patients could tolerate. Other reports indicate that daily infusions of 600 ml. of Lipomul I. V. given for 14 consecutive days and totalling 8,400 ml. are well tolerated by adult patients.[7,11,17]

The present study was undertaken to further define the limitations of intravenous infusions of fat in patients requiring nutritional supplements for long periods. Since bleeding seems to be a characteristic feature of the fat-overloading syndrome, patients were observed for clinical evidence of a hemorrhagic tendency and attention was centered on a study of blood coagulation.

Methods

A fat emulsion (Lipomul I. V. of the 11-612 series) was given to 20 hospitalized patients, all of whom were unable to eat a diet sufficient to maintain weight. There were 19 men and 1 woman. Ages were from 33 to 69 years. The diagnosis in 10 patients was advanced neoplasm. In four, it was malnutrition following gastric resection. One each had the following diagnoses: meningioma, Parkinson's syndrome, postoperative gastric resection for peptic ulcer, chronic pancreatitis, diverticulitis of the colon, and pelvic abscess with osteomyelitis. One patient (Patient 15, Table 2) received fat

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* Lipomul I. V., The Upjohn Company.

emulsions for three weeks immediately preceding a gastroenterostomy. Five patients began their series of infusions within nine days following a major operative procedure. There was no clinical evidence of a hemorrhagic tendency in any patient prior to administration of the infusions.

Other medications, including vitamins, antibiotics, plasma, blood transfusions, and solutions of electrolytes were given to these patients when indicated during the periods when the fat emulsions were given.† No other intravenous infusions were given at the same time or through the same tubing as the emulsion.

Nineteen patients were given 21 consecutive daily infusions of 500 ml. of Lipomul I. V. in 21 days, and one patient received 34 infusions in 30 days. The time during which a unit of fat emulsion (500 ml.) was given was approximately two hours. The infusions were well tolerated, and, although minor reactions occasionally occurred, none were severe enough to warrant discontinuation of the infusion.

Blood coagulation and other tests listed in Table 1 were done before and at weekly intervals (or more often) during and after courses of infusions. In two of three patients who hemorrhaged, the blood was tested for circulating anticoagulants by the protamine titration test.[6] Blood was usually drawn for these tests early in the morning with the patient fasting. Thus, during the courses of infusions, tests were made approximately 22 hours after completion of the infusion given the preceding day. Since the coagulation of blood is altered by a lipemia induced by intravenous fat,[10] the serum turbidity was determined daily in all patients by means of per cent transmission of light, using a Coleman photoelectric colorimeter with a filter of mean wave length of 655 mμ. Although the fasting serum became abnormally turbid in all 20 patients at one time or another during the period of infusion, the turbidity was of slighter degree than that observed by Mandel and associates during fat-emulsion-induced lipemia.

Syringes and glassware used for the collection of blood and for the performance of clotting tests were siliconized with General Electric Silicone Dri-Film. Needles were siliconized with Arquad 2C.

Whole Blood Clotting Time.—This test is a gross measurement of the over-all coagulability of blood. Blood was drawn with a 19-gauge needle attached to a 5 ml. syringe. Care was taken to obtain freely flowing blood by clean venipuncture and to avoid air bubbles. After withdrawal of 5 ml. of blood, the syringe was removed and a 20 ml. siliconized syringe attached and 20 ml. of blood withdrawn. One milliliter of this blood was gently inserted into each of three test tubes and placed in a water bath at 37 C. The first tube was tilted 15 minutes later and every minute thereafter until clotting occurred. The second tube was then tilted, and when it was clotted the third tube was tilted at one-minute intervals. The clotting time was the interval from the first appearance of blood in the syringe to the formation of a clot in the tube in which the clotting was slowest. Blood from the 5 ml. syringe and the remaining blood in the 20 ml. syringe was used for the other tests.

Coagulation Time of Recalcified Plasma.—This test is also a measure of the over-all coagulability of blood. The test was performed as described by Quick, using samples of plasma obtained by centrifugation at different rates of speed. The plasma for Test 1 is centrifuged at low speed, and for Test 2 at high speed.

Prothrombin Consumption.—This test is a measure of the factors that produce thromboplastin and thus reflects abnormalities in the first stage of clotting. Quick's method was used, except that Symplastin‡ instead of acetone-extracted rabbit brain was used as thromboplastin.

Clot Retraction and Quality of Clot Strength.—Clot retraction was observed 8 and 24 hours after collection of 5 ml. of blood in a siliconized tube. Normally, there is a maximum clot retraction in 24 hours. Clot strength was tested by picking up each clot with a fine tissue forceps 8 and 24 hours after clotting and observing the friability of the clot.

Prothrombin Time.—This is a measure of the prothrombin complex, including Factors V and VII.

† The emulsions contain 15% cottonseed oil, 4% dextrose, 1.2% soybean phosphatide and 0.3% polyoxalkol (Pluronic F-68).

‡ Warner-Chilcott.

TABLE 1.—*Blood Coagulation and Other Tests* *

	Normal Value
Whole Blood Clotting Time (3-tube Lee & White method, see text)	24 to 57 min. †
Coagulation Time of Recalcified Plasma (Quick,[14] p. 363)	Test 1, 2.5 to >60 min † Test 2, 3.2 to >60 min. †
Prothrombin Time (Quick,[14] p. 379)	70% to 100%
Prothrombin Consumption (Quick[14])	
Clot Retraction and Quality of Clot Strength (see text)	
Fibrinolysin (Quick,[14] p. 438)	No clot lysis in 48 hr.
Plasma Fibrinogen (Cullen & Van Slyke)	0.4-0.6 gm. per 100 ml.
Blood Platelets (Quick,[14] p. 367)	300,000-500,000 per cu. mm.
Fasting Serum Turbidity (see text)	90% to 100% transmission

* These tests were run in all patients except the prothrombin consumption test, which was run in 6 patients and blood fibrinogen, which was determined in 4 patients.

† Preinfusion values instead of normal values are given.

TABLE 2.—*Effect of Daily Fat Infusions on Blood Coagulation**

Patient	Diagnosis	No. of Infusions 500 Ml. Each	Clotting Time, Minutes		Recalcification Test No. 1, Minutes		Prothrombin Time, % Normal	
			Before	After	Before	After	Before	After
1	Metastatic cancer	21	30	300 (34)	10.3	10.0 (31)	82	10 (34)
2	Cancer of the pancreas	34	15	>120 (32)	2.5	7.4 (31)	100	18 (32)
3	Cancer of the tongue	21	40	131 (44)	4.5	8.4 (17)	60	40 (22)
4	Meningioma	21	55	175 (29)	3.6	11.8 (51)	52	60 (44)
5	Cancer of the pancreas	21	54	116 (26)	10.8	4.7 (22)	100	43 (22)
6	Parkinson's disease	21	26	97 (22)	3.4	5.8 (31)	94	22 (31)
7	Cancer of the colon	21	56	90 (32)	6.3	6.6 (22)	43	50 (22)
8	Abscess osteomyelitis	21	53	88 (38)	10.5	9.9(108)	71	60 (38)
9	Postop. total gastrect.	21	75	85 (17)	12.3	2.3 (17)	100	60 (17)
10	Diverticulitis	21	46	76 (7)	11.1	17.8 (29)	60	50 (7)
11	Cancer of the colon	21	40	72 (22)	4.0	8.4 (56)	—	71 (11)
12	Pancreatitis	21	36	63 (7)	6.2	8.2 (21)	85	60 (21)
13	Cancer of the colon	21	26	63 (22)	5.1	8.7 (22)	60	60 (22)
14	Postop. gastrectomy	21	35	60 (22)	3.4	10.9 (21)	75	60 (44)
15	Cancer of the pancreas	21	43	56 (22)	4.4	8.9 (12)	100	50 (34)
16	Cancer of the colon	21	25	55 (28)	>60	11.7 (22)	—	58 (28)
17	Postop. subtot. gastrect.	21	26	48 (29)	5.7	9.1 (22)	100	60 (22)
18	Postop. total gastrect.	21	36	48 (22)	3.6	5.8 (39)	50	45 (22)
19	Postop. total gastrect.	21	57	34 (19)	3.8	10.8 (21)	75	75 (21)
20	Cancer of the colon	21	54	24 (11)	4.8	12.5 (61)	100	60 (11)

* Figures in parentheses indicate the time in days from the start of the infusions that the most abnormal value was observed, i. e., "(7)" indicates the seventh day of infusions at which time the patient had received 6 units; "(44)" indicates the 44th day after the start of the infusions and 23 days after the last of 21 infusions.

The Quick one-stage prothrombin time was used. Symplastin ‡ was used as thromboplastin.

Fibrinolysin.—This was determined by Quick's method. The test determines the presence of circulating enzymes with fibrinolytic properties. Normally, the plasma remains clotted and does not lyse in 48 hours. The rapidity of lysin provides a gross index of the amount of fibrinolysin activity present.

Results

The only serious effect of daily administration of 500 ml. of Lipomul I. V. to these patients was hemorrhage, which occurred in three patients. No other patient developed symptoms or signs on physical examination suggestive of fat-overloading syndrome or of hemorrhagic tendency. Pain in the abdomen and enlargement of the liver and spleen were not noted. No abnormal accumulation of fat was detected on ophthalmoscopic examination of the retina in five patients.

An exploratory laparotomy and gastroenterostomy was done in one patient (Patient 15, Table 2) after the last of 21 daily infusions. No abnormal bleeding or oozing was noted by the surgeon. Laboratory tests 48 hours prior to surgery were as follows: whole blood clotting time, 56 minutes; plasma recalcification time, Test 1: 5.9 minutes; Test 2: 12.5 minutes; prothrombin content, 60% of normal; clot retraction poor and quality of clot strength weak; fibrinolysin test: lysis of clot in four hours; serum turbidity, 55% transmission.

The test which was most consistently and markedly altered was the whole blood clotting time. Preinfusion values for this test ranged from 15 minutes to 57 minutes (with the exception of one patient in whom it was 75 minutes). Increase in the clotting time during or after the infusions as compared with the initial value was noted in 18 of 20 patients. In 14 patients, the clotting time became prolonged to one hour or more, and in three it became prolonged to more than two hours. In three patients who hemorrhaged, clotting times at the time of hemorrhage were 175, >200, and 300 minutes. Maximum prolongation of the clotting time in most cases was observed between 20 and 35 days after beginning the infusions.

The plasma recalcification time (Test 1) became increased above preinfusion levels in 15 patients and showed no change or was decreased in the other 5 patients. In general, changes in plasma recalcification paralleled those observed in the whole blood clotting times. Since the clotting of both samples of plasma (Tests 1 and 2) were approximately the same, only the results of Test 1 are given in Table 2.

Blood prothrombin content was within normal limits prior to the infusions in 12 patients (of the remaining 8, it was abnormally low initially in 6 or not determined in 2). Eleven of the twelve patients had a decrease in prothrombin content during or after the infusions to levels ranging from 10% to 60% of normal. Most frequently, this was noted between 20 and 30 days after the start of the infusions (Table 2).

Clot retraction and quality of clot strength were normal prior to the infusions in all patients and became decreased during or after the infusions in 16 patients. In these patients, the clot became abnormally soft, friable, and showed little or no retraction. This was a progressive change and usually became apparent after 14 days of infusions.

Fibrinolysin was normal prior to the infusions in all patients. Increased fibrinolysin activity during or after infusions occurred in 10 patients.

Prothrombin consumption showed considerable variation before, during, and after the infusions in the six patients in whom it was studied. No conclusions could be drawn from this test.

Platelet counts fell to abnormally low levels in 10 patients and in 10 remained at normal or at preinfusion levels. This decrease was noted 14 to 30 days after the infusions were begun.

Fibrinogen was determined in four patients and was within normal limits before, during, and after the infusions.

The turbidity of fasting serum increased in all patients as a result of the infusions. In most cases, this change was slight (less than 20% transmission as compared with preinfusion levels) and did not occur until after 14 and usually 17 infusions. In five patients, the turbidity fell below 70% transmission. In one patient (Patient 2, Table 2; Fig. 2) the fasting serum became abnormally turbid during the first week of infusions and became increasingly turbid until the 28th day, at which time there was 22% transmission of light as measured on the photometer. When the infusions were discontinued, there was gradual return to preinfusion turbidity during a five-day period.

Two patients developed microscopic hematuria during the period of infusions. One patient (Fig. 1) had gross hematuria in association with hemorrhage. The hematuria cleared with return of coagulation toward normal in two patients but continued for at least four weeks in the third patient (Fig. 3).

In nine patients, the effect of fat infusions on the blood hemoglobin levels could not be evaluated because these patients had anemia related to advanced cancer, had received blood transfusions, or had suffered blood loss incident to a surgical operation. In 11 patients in whom evaluation of hemoglobin was possible, the hemoglobin varied from 11.7 gm. % to 16.2 gm. % prior to the infusions and remained within this range during and after the infusions.

Case histories of three patients who hemorrhaged are as follows:

PATIENT 1 (Fig. 1).—A 59-year-old man had undifferentiated metastatic carcinoma of the dorsal spine and paraplegia. He received 21 daily infusions. Twelve days after the last infusion, hemorrhaging began from his gastrointestinal and genitourinary tracts. His fasting serum turbidity at this time was 83% transmission. The whole blood clotting time was 300 minutes. There was an increase in plasma recalcification time. The prothrombin content was 10% of normal. The platelets were 130,000 per cubic millimeter. Fibrinolysin was normal. Clot retraction was poor and clot strength was weak. Protamine titrations run on three occasions during the two days while the patient was hemorrhaging revealed no evidence of heparinemia. The hemorrhage stopped after 2,500 ml. of blood was given as transfusions and did not recur during a two-month period of follow-up.

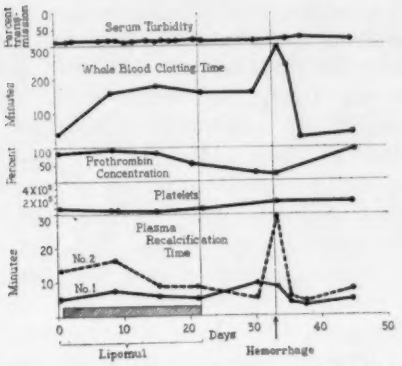

Fig. 1 (Patient 1).—Effect of continued daily infusions of a fat emulsion on serum turbidity and blood coagulation; 500 ml. of Lipomul I. V. was given daily for 21 days.

PATIENT 2 (Fig. 2).—This 46-year-old patient had a diagnosis of carcinoma of the pancreas established at laparotomy by biopsy. Fat emulsions were begun 24 days after the laparotomy and were continued for 30 days. During the last four days, he received two units per day for a total of 34 units. On the last day of infusions, he had hematemesis and melena and bled from venipuncture wounds and venoclysis cut-downs. At the time of hemorrhage, his fasting serum turbidity was 22% transmission. The whole blood clotting time was over two hours and the prothrombin content was 18% of normal. Platelets were 35,000 per cubic millimeter. The plasma recalcification time and fibrinolysin were increased. Protamine titration on three occasions during a two-day period when the patient was hemorrhaging were negative for circulating anticoagulants. The hemorrhages stopped after the transfusions of 6,500 ml. of whole blood given over a four-day period. Clotting tests returned to normal or preinfusion levels after the transfusions. The patient survived for one month and died of carcinoma.

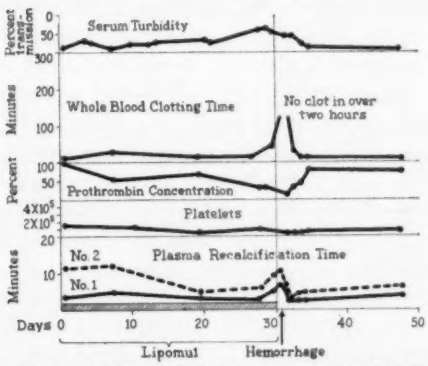

Fig. 2 (Patient 2).—Effect of continued daily infusions of a fat emulsion on serum turbidity and blood coagulation; 500 ml. of Lipomul I. V. was given daily for the first 26 days and 1,000 ml. for the following 4 days.

PATIENT 3 (Fig. 3).—This 58-year-old white man with carcinoma of the tongue refused surgery. He gained weight on fat emulsions. Microscopic hematuria was noted on the 15th day of infusion and continued for at least four weeks thereafter. He hemorrhaged from the ulcerated tongue lesion 21 days after the last of 21 infusions. At this time, his whole blood clotting time was prolonged to 130 minutes. His prothrombin concentration was 75% of normal. Fibrinolysin was normal. Clot retraction was poor and clot strength was weak. Fasting serum turbidity was 85% transmission. Platelets were 20,000 cu. mm. Two units of blood restored hemostasis temporarily. Further transfusions were withheld, and he hemorrhaged again from his tongue and died several days later.

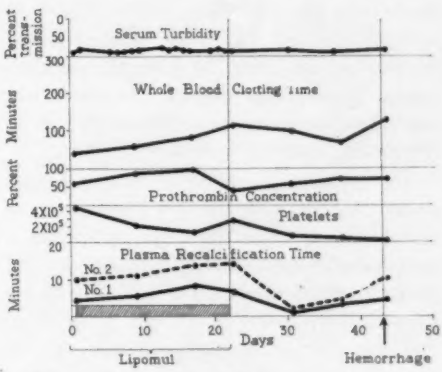

Fig. 3 (Patient 3).—Effect of continued daily infusions of a fat emulsion on serum turbidity and blood coagulation; 500 ml. of Lipomul I. V. was given daily for 21 days.

Follow-Up of Patients.—Serum turbidity and coagulation tests were done in all except one patient (Patient 19, Table 2) following the last infusion of fat. In five of the patients (Patients 5, 12, 13, 16, and 17, Table 2), these tests were done seven days after the last infusion. In the remaining 14 patients, the follow-up period extended from 7 to 90 days, during which tests were done at intervals. Ten of these were followed by tests at approximately weekly intervals as follows: two for three weeks, three for four weeks, one for five weeks, one for six weeks, and three for seven weeks after the last infusion. The hypocoagulabil-

ity of the blood observed in these 14 patients reverted to normal or to preinfusion status in all, usually within three weeks after the last infusions. Serum turbidity returned to preinfusion levels in a week or less after the last infusion.

Comment

Although the toxic effects of intravenous infusions of fat have been studied in detail, the effects of fat emulsions on blood coagulation have received little attention. Mandel and associates found that a single infusion of Lipomul I. V. caused hypercoagulability of the blood as determined by the whole blood clotting time and Stypven plasma clotting time, when these tests were run during the phase of lipemia. This acceleration of clotting was more marked in 11 healthy persons than in 9 hospitalized patients. Hypercoagulability of the blood was also observed to occur at the height of an alimentary induced lipemia.[2,4,10,13,14]

The hypercoagulability of blood (accelerated clotting) induced by a single infusion and occurring when the serum is lipemic is in contrast to the hypocoagulability (delayed clotting) which occurs as a result of consecutive daily infusions of fat. It is to be noted that the coagulation tests reported in the present studies were run on fasting blood so as to minimize the effect of lipemia and so that these opposite effects of fat infusion on blood coagulation would not be confused.

Since no significant changes in blood coagulation occurred in patients until after 14 consecutive daily infusions of 500 ml. or more, it appears that this amount may be safely administered without the necessity for control coagulation tests.

The finding of hypocoagulability on laboratory tests in most patients and the occurrence of hemorrhage in three patients who had been given 21 daily infusions indicated that this amount should not ordinarily be administered. In special situations, when intravenous fat is required for more than 14 days, blood coagulation tests should be done at frequent intervals. The whole blood clotting time, prothrombin time, platelet count, and microscopic examination of the urine for blood cells can serve as a guide to the clinician and should reveal hypocoagulability before hemorrhage occurs. If these tests become abnormal, the emulsion should be discontinued and the patient kept under observation until the hypocoagulability has reverted toward normal. This may not occur until a week or more after the last infusion. Should hemorrhage occur, transfusions of whole blood are recommended. In three patients in our series who hemorrhaged, there was prompt return of blood coagulability to normal and cessation of hemorrhage when transfusions were given.

The occurrence of severe hemorrhage in 3 of 20 patients is in accordance with the experience reported by Artz, who gave 1,200 ml. of Lipomul I. V. to seven patients for 11 to 21 days. Four of these developed spontaneous hemorrhage.

Fat-overloading syndrome described by others [8,11,18] did not develop in any patients studied by us. It thus appears that the hemorrhagic tendency can occur without the other features of the syndrome and may be the earliest symptom to appear. Hypocoagulability of the blood as detected by laboratory tests should be a warning that fat-overloading syndrome may occur and indicates that further infusions of fat should not be given until these tests have returned to normal.

These studies have not served to define the mechanism of the clotting defect caused by fat infusions. Negative protamine titration tests in the patient who hemorrhaged indicated that an endogenous heparinemia did not occur. Low blood fibrinogen levels were not encountered. The findings of normal number of platelets in some patients, thrombocytopenia in others, normal prothrombin content in some, and hypoprothrombinemia in others suggest that the mechanism is complex and may not be the same for all patients.

Summary

Twenty hospitalized patients were given daily intravenous infusions of 500 ml. of a fat emulsion for 21 days or longer.

Hypocoagulability of the blood occurred in most patients, and severe hemorrhage occurred in three.

The hypocoagulability was temporary and reverted to normal without treatment within several weeks after the infusions were discontinued except in three patients in whom it was corrected with transfusions.

Five hundred milliliters of a fat emulsion (Lipomul I. V.) may be given safely for 14 consecutive days to adult patients, but hypocoagulability of the blood may develop from fat in excess of this amount.

333 E. Huron St. (11).

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DISCUSSION

DR. JACK COLE, Cleveland: In 1953, when Lipomul was undergoing early clinical investigation, we became interested in its effects on platelets, and found that the platelet count was depressed following administration, substantially in agreement with the work of Dr. Werr and Dr. Preston. I have two slides that summarize this work.

[Slide] This slide shows a series of six experiments in which we administered the early intravenous Lipomul preparation. The column on the left indicates the preinfusion platelet count and indicates the amount of the Lipomul emulsion that was administered.

The maximum amount given was 500 cc. When the Lipomul was discontinued a platelet count was obtained, as shown in the column on the right, and you will see that in all six experiments (with the exception perhaps of the second one) there was a significant fall in the platelet count, occurring anywhere from 5 hours and 15 minutes to 1 hour and 30 minutes, following the Lipomul infusion.

[Slide] This shows the per cent of fall in platelet counts in a group of persons in whom we had produced a hyperlipemia by the alimentary administration of Lipomul, and we were interested in the fact that heparin, when administered to patients who had exhibited a fall in their platelet

count, was able to clear the hyperlipemia transiently and also elevate the platelet count. However, after the effect of heparin had been dissipated, the platelet counts again fell.

DR. EDWIN H. ELLISON, Milwaukee: Once again we are indebted to Drs. Werr and Preston for bringing us additional information on this latest addition to our nutritional know-how.

Our experience has not been as extensive as theirs, but we have given over 200 units of Lipomul to some 30 patients in amounts varying from 1 to 28 units. Study of the platelets, blood clotting time, bleeding time and prothrombin activity, and the morphology of the cellular elements including bone marrow examination, we carried out with very similar findings reported by Drs. Werr and Preston.

Eight of these patients received daily infusions of the material for as long as two weeks, and of these, five showed some alteration of their blood coagulability. One developed massive hemorrhage—a patient with a severe burn.

As has already been pointed out, the exact mechanism of these changes is unknown. This is not surprising, since the mechanism of normal coagulation itself has not been completely worked out. The failure of clot retraction does suggest some alteration of the thromboplastin and platelets. The lowered prothrombin values might well mean a transient decrease in liver function, and I would like to ask Dr. Werr if this finding could be prevented by parenteral vitamin K.

Another thing comes to mind. In the last few months I have had the opportunity of working with Dr. Quick, who has a favorite theory that coagulation is not a hemostatic mechanism but basically a wound-healing mechanism, and I would like to ask Dr. Werr if he has noted any changes in wound healing in the patients who went to surgery.

Finally, this report should not be interpreted to mean that we should not utilize intravenous fat, since this is the only method available for us for total parenteral nutrition. The number of severe complications resulting from malnutrition still far outweigh the trouble seen with this material.

DR. WILLIAM E. ABBOTT, Cleveland: I believe that it is important to emphasize that Dr. Wretlind and his associates at the Karolinska Institute in Stockholm have been able to cause death and a marked anemia in dogs by overloading them with fat. In most of the experiments by his group they noted that a dog could tolerate up to 4.5 to 5 gm. of fat per kilogram of body weight per day. When they were given amounts of fat at this level or in slight excess, death usually occurred in from 7 to 20 days. The long-term reactions to intravenous infusions of fat which have been reported have usually occurred in patients who were given a large excess of fat on a per kilogram of body weight basis such as the patients first reported by Dr. Stanley Levenson at Walter Reed Hospital and Dr. Donald Watkins at the National Institutes of Health. Other groups have also seen a similar serious long-term reaction, and in most of these reports the oral fat intake and the size of the patient were not noted. However, it can be presumed that many of them got a fairly large and probably an excessive amount of fat on a per kilogram of body weight basis. In other instances there were often deficiencies of essential nutrients, such as vitamins, proteins, and certain minerals, which might have produced an intolerance to the emulsion or led to bleeding, fever, and other reactions. In many instances the patients studied have been ill and undernourished patients with incurable cancer and might well be more susceptible to reactions, and thus the significance of some of these reports is difficult to evaluate. Certainly this type of patient, who would never be given fat intravenously under normal circumstances, is a poor subject to study. It is our present feeling that it is wise to give about 2.5 gm. of fat per kilogram of body weight per day. This should include both the oral and intravenous intake, and it should never be given without other more essential nutrients, such as minerals, vitamins, and proteins. Our studies have shown that the administration of fat without protein offers the patient very little that the administration of 100 to 200 gm. of sugar would not accomplish. We believe that it also should be stressed that the only value of fat is as a source of calories, and therefore it should not be used in the desperately ill and dying patient with hope of producing some miracle with life-saving benefits.

I enjoyed the presentation of Drs. Werr and Preston, and in closing I would like to stress the fact that it is easy to provide 1,400 to 1,600 calories by giving protein hydrolysates and sugar-containing solutions, and it is only the occasional patient who will derive benefit from the administration of an additional 750 calories from the intravenous infusion of a fat emulsion. At present we believe this form of therapy should be reserved primarily for those patients who are markedly undernourished and have to undergo fairly extensive surgery or patients who can not take oral nutrients for a prolonged period of time following an operation.

DR. FREDERICK W. PRESTON, Chicago: I would like to answer Dr. Ellison's questions.

We have not studied vitamin K in relation to these blood coagulation defects, nor have we observed any ill effect of the administration of fat emulsion on wound healing. We have operated on a number of patients who have had Lipomul during their preoperative preparation, and I think if there had been any marked effect we would have observed it.

The work reported by Dr. Werr today followed a previous study made in our laboratories concerning the effect of lipemia on blood coagulation. A number of clinicians have been interested in this problem and have been able to demonstrate hypercoagulability following meals containing as little as 12 gm. of fat. The effect of an alimentary induced lipemia on blood coagulation is slight, and at least three groups of investigators have failed to confirm that hypercoagulability is produced in this manner (Manning, P. R., and Walford, R. L.: Lack of Effect of Fat Ingestion on Blood Coagulation, *Am. J. M. Sc.* 228:652-655, 1954; Sohar, E.; Rosenthal, M. C., and Adlersberg, D.: Plasma Lipids and Coagulation in Blood, *Am. J. Clin. Path.* 27:503-514, 1957; Tulloch, J. A.; Overman, R. S., and Wright, I. S.: Failure of Ingestion of Cream to Affect Blood Coagulation, *Am. J. Med.* 14:674-680, 1953). In our experience a more marked lipemia resulted when 100 to 150 ml. of fat emulsion (Lipomul I. V.) was given intravenously than when 300 ml. of 36% whipping cream was given orally, and the changes in blood coagulation were more marked (Mandel, E. E.; Hunter, L. M.; Preston, F. W., and Silverman, M.: Effect of Fat-Loading upon Blood Coagulation, *Am. J. Clin. Path.* 30:11-18, 1958). The importance of these findings lies in the possibility that this hypercoagulability may lead to intravascular thrombosis under conditions where there is slowing or eddying of the blood flow. It also has been suggested that these changes in clotting may play a role in the etiology of atheroma by enhancing formation of fibrin in the circulating blood and its subsequent deposition beneath its vascular endothelium. This hypercoagulability can be prevented by adequate bishydroxycoumarin (Dicumarol) therapy (Mustard, J. F.: Increased Activity of the Coagulation Mechanism During Alimentary Lipemia: Its Significance with Regard to Thrombosis and Atherosclerosis, *Canad. M. A. J.* 77:308-314, 1957).

In contrast to this accelerated clotting which occurs when the blood is lipemic is the decreased tendency to clot which results from repeated infusions of fat. Dr. Werr's work indicates that this occurs in most patients given 500 ml. of Lipomul I. V. for 21 days or more.

Although we did not define the exact factor or factors responsible for the hemostatic defect in these patients, it is of practical importance that transfusions of whole blood stopped the hemorrhage in three patients and returned their coagulation tests to normal or nearly so. Whole blood contains adequate fibrinogen, platelets, prothrombin, and prothrombin precursors. These substances deteriorate as the blood ages, and platelets disintegrate on contact with air and glassware. Therefore when transfusions are used in the emergency treatment of hemorrhage associated with hemostatic defects in which multiple or unknown coagulation factors may be involved, fresh whole blood, preferably drawn in plastic containers, is an effective method of treatment.

Dr. Werr mentioned fat overloading syndrome. There are now on record 10 cases of this syndrome resulting from the use of Lipomul I. V. These have occurred among 70 persons who have received the emulsion in amounts ranging from 15 to 70 units (500 ml. each) (J. B. Lawson, personal communication). Bleeding, particularly from the gastrointestinal tract was one of the features of the syndrome. Dr. Werr's work indicates that changes in blood coagulation may be detectable before bleeding occurs and that these changes may occur without the other features of the syndrome.

Fat emulsions have been an important addition to the pre- and postoperative management of malnourished patients undergoing major surgical procedures. We now use these substances routinely in our institution for such patients. Dr. Werr's work has served to further define the limitations of these emulsions, and, as he has said, we currently believe that only in unusual circumstances should a patient receive more than 14 consecutive daily infusions of 500 ml. of fat emulsion. His experience indicates that a second series of 14 daily infusions may be given after an interval of two, and preferably three, weeks.

Open Heart Surgery for Acquired Mitral Insufficiency

F. HENRY ELLIS Jr., M.D.; ROBERT O. BRANDENBURG, M.D.; JOHN A. CALLAHAN, M.D., and HIRAM W. MARSHALL, M.D., Rochester, Minn.

Since the successful clinical introduction of extracorporeal circulation [1] in 1953, the majority of operations performed with the aid of this technique have been for congenital heart disease. Open heart surgery for acquired heart disease has developed more slowly, and mitral insufficiency, among other acquired valvular defects, only recently has come under direct surgical attack. Until relatively recently, pure mitral insufficiency was considered a rarity and of debatable significance with regard to cardiac function. We now know that mitral insufficiency, although less common than mitral stenosis as a predominant lesion, is a recognizable entity and can be a progressive disabling disease.

The anatomic factors which may underlie incompetence of the mitral valve are many and complex. They have been reviewed in some detail by Edwards and Burchell [2] and need not be repeated here. It is of importance, however, to recognize that "mitral insufficiency begets mitral insufficiency." That is to say, with the initiation of incompetence of the noncalcified mitral valve a series of events are set into motion which lead only to greater and greater degrees of incompetence and regurgitation. To the original lack of valvular tissue may be added dilatation of the left atrium and mitral ring and separation of the papillary muscles. All these developments lead only to further separation of the valve leaflets and a self-perpetrating vicious cycle. Experimental studies from our laboratory,[3] as well as clinical experience with cases of mitral insufficiency, attest to the truth of this view. Not only does this concept have significance with regard to the life history of the disease, but it also must be taken into account when one is undertaking surgical correction of the defect and is evaluating long-term results.

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Section of Surgery (Dr. Ellis); Section of Medicine (Drs. Brandenburg and Callahan), Mayo Clinic and Mayo Foundation. Fellow in Physiology (Dr. Marshall), Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

Surgical Procedures

A variety of surgical procedures have been employed clinically in past years in corrective and palliative attempts to treat incompetence of the mitral valve. These have included the use of hammocks and slings of vein,[4] vein-covered tendon grafts,[5] pericardial grafts,[6,7] valvular suture,[7] and the intracardiac placement of plastic baffles and obturators.[8,9]

These methods have been largely abandoned owing to technical difficulties associated with their proper positioning in the left atrium and left ventricle, the unsuitability of the materials used, and the high mortality accompanying their utilization. Pericardium disintegrates to functionally valueless fibrous cords,[7,10,11] and foreign materials frequently become the sites of infection or the sources of fatal emboli.

Failure of the foregoing procedures led to the clinical use of methods designed to narrow the mitral annulus either by direct suture approximation of the annulus in the region of one of the commissures [12,13] or by circumferential suture of the mitral valve.[14] In our laboratory studies of the latter technique on dogs with chronic mitral insufficiency demonstrated a marked tendency for recurrence of the insufficiency after correction.[15] This discouraged us from em-

TABLE 1.—*Summary of Clinical Aspects of 15 Patients Operated on for Mitral Insufficiency* *

			History				Apical Murmurs		ECG		Surgery: Findings			Surgery: Procedure			
Patient	Age, Yr.	Sex	Duration, Yr.	SBE	RF	N. Y. H. A., Class	Systolic	Diastolic	AF	LVH	Dilated Ring	Deficient Tissue	Ruptured Chordae	Annuloplasty	Ivalon	Leaflet Plication	Result
1	23	M	8	0	+	III	+	+	+	+	+	+	0	+	0	0	Functionally excellent; recurrent mitral insufficiency at recatheterization
2	28	F	14	0	+	III	+	+	+	0	+	+	0	+	0	0	Excellent
3	44	M	4	0	0	II+	+	0	0	+	+	0	+	+	0	0	Functionally excellent; recurrent mitral insufficiency at recatheterization
4	45	F	8	0	+	IV	+	+	+	+	+	+	0	+	0	0	Excellent
5	46	F	13	0	+	IV	+	+	+	+	+	+	0	+	0	0	Improved
6	49	M	2	0	0	IV	+	0	+	0	+	0	+	+	0	0	Excellent
7	48	F	16	0	+	II+	+	+	+	+	0	0	+	+	0	+	Hospital death
8	40	M	4	0	0	III	+	+	+	+	0	+	0	0	+	0	Late death
9	26	F	1	0	+	III	+	+	+	+	+	+	0	+	0	0	Hospital death
10	52	M	½	0	+	III	+	0	+	+	0	0	+	0	0	+	Excellent
11	35	M	3	0	+	IV	+	+	+	+	+	+	0	+	0	0	Excellent
12	31	F	9	0	+	III	+	+	+	+	0	+	0	0	+	0	Hospital death
13	26	M	½	+	+	III	+	+	+	+	0	0	+	0	0	+	Survived; too early to evaluate
14	47	F	7	0	+	III	+	+	+	0	0	+	0	0	0	+	Survived; too early to evaluate
15	42	M	1	0	0	III	+	0	+	+	+	+	0	+	0	+	Survived; too early to evaluate

* Abbreviations used: SBE=Subacute bacterial endocarditis; RF=rheumatic fever; AF=auricular fibrillation; N. Y. H. A.=New York Heart Association Classification; LVH=left ventricular hypertrophy.

ploying the technique clinically. Similar unsatisfactory results in a large group of patients have been reported recently by Kent and associates.[16]

The concept of narrowing of the dilated mitral ring is a logical one, however, and with the aid of extracorporeal circulation the procedure can be carried out accurately under direct vision and any other indicated procedure can be performed. Several encouraging reports have appeared recently concerning this approach.[17-21] Lillehei [22] has reported an operative mortality of 15% in 27 patients. Although the reports just mentioned are enthusiastic about the results of open heart operations in the management of patients with mitral insufficiency, little objective data have been presented on the initial or long-term postoperative result. The purpose of this presentation is to review our experience with operations for acquired mitral insufficiency. Particular emphasis will be placed on the operative and postoperative hemodynamic findings in order better to delineate the place of this operation in the clinical management of patients with this disease.

Preoperative Data

Clinical.—A total of 15 patients form the basis of this report; data on 6 of them have been briefly reported previously.[23] There were seven women and eight men (Table 1). The ages ranged from 23 to 52 years. Only one patient gave a history of bacterial endocarditis, although five proved to have ruptured chordae tendineae as the cause of the mitral insufficiency. Eleven had had rheumatic fever, including the one patient who had bacterial endocarditis. Two patients were placed in Class II according to the New York Heart Association Classification of cardiac function, although both had greater than mild limitation of function; nine patients were placed in Class III, and four in Class IV. The duration of significant limitation of exertional capacity varied from 3 months to 16 years. Four of the five patients who were found to have ruptured chordae tendineae had had these symptoms for two years or less. The fifth patient, however, had had symptoms for 16 years.

All patients were found to have a loud, pansystolic murmur at the apex. In 2 patients, the intensity of the murmur was graded 2 (on a grading basis of Grade 1 to 4) and in the other 13 patients was graded 3. A systolic thrill was noted in almost half of the patients. Of the 15 patients 11 had apical diastolic murmur, and only 2 of these had significant mitral stenosis. In most, the murmur was short in duration and confined to the early diastolic period. In three of these patients, however, a diastolic thrill was noted. In one patient who had significant mitral stenosis, the murmur was heard throughout most of diastole. An apical systolic thrust was noted in 9 of the 15 patients. This is an important sign of left ventricular hypertrophy and deserves emphasis.

The murmur of mitral insufficiency is usually transmitted to the left axilla. In some instances, when the posterior leaflet is involved, the murmur may be transmitted mainly to the base of the heart and may simulate the murmur of aortic stenosis.[24,25] In three of the five patients who had ruptured chordae tendineae, the posterior leaflet was involved and a prominent basal systolic murmur was noted.

Of the 15 patients 14 had auricular fibrillation at the time of operation, and 12 of the 15 had electrocardiographic evidence of left ventricular hypertrophy. One patient had incomplete left bundle-branch block. None of the patients had electrocardiographic evidence of right ventricular hypertrophy.

Roentgenographic evidence of cardiac enlargement which was present in each patient seemed to involve primarily the left ventricle and left atrium. In many patients, the cardiac shadow was huge, owing particularly to the marked atrial enlargement (Fig. 1). Evidence of calcification of the valve was searched for at cardiac roentgenoscopy and in oblique roentgenographic views of the thorax but was not noted with

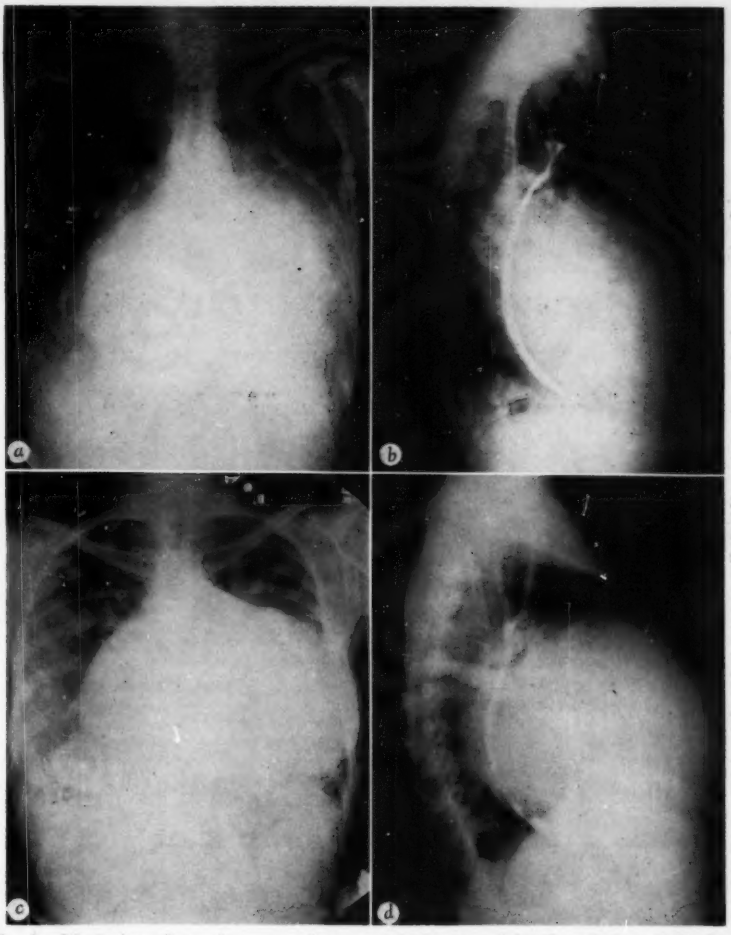


Fig. 1.—Marked cardiac enlargement in two patients. (*a* and *b*) Case 5. (*c* and *d*) Case 12.

certainty in any instance. Similar observations have been reported by Ross and associates.[26]

Hemodynamic.—Data obtained at cardiac catheterization are presented in Table 2. The diagnosis of pure or predominant mitral insufficiency was made during right heart catheterization in nine patients. Supplementary left heart and aortic catheterization were required in two patients to exclude coexisting aortic insufficiency. In general, the diagnosis of severe mitral insufficiency was established on the basis of the contours of the pulmonary artery wedge-pressure pulse and indicator-dilution curves.[27,28] In four of the 11 patients, wedge pressures were not obtained; however, the indicator-dilution curves in these patients supported the clinical diagnosis of severe mitral insufficiency. Examples of pressures and indicator-dilution curves obtained prior to operation are shown in Figures 2, 3, and 4.

Surgical Aspects

Approach.—Two surgical approaches were employed in this group of 15 cases. In two of the early cases a bilateral, anterior thora-

TABLE 2.—*Hemodynamic Data During Cardiac Catheterization Before and After Correction of Mitral Insufficiency* *

Case	Age, Yr.	Sex	Surface Area, Sq. M.	Time of Catheterization	Average Pressures, Mm. Hg				Mixed Venous Blood, Per Cent Saturation	Cardiac Index, L/Min/Sq. M.	Resistance, Dynes Sec. Cm. $^{-5}$		
					Right Atrium	Pulmonary Artery	Wedge	Systemic Artery			Total Pulmonary	Pulmonary Arteriolar	Systemic
1	23	M	1.73	Preop.	21/9	81/6-13 †	17/6	125/77	50	2.2	--	--	2,060
				19 days P. O.	7/2	39/15	18/11	136/63	67.5	3.1	350	195	1,400
				7 mo. P. O.	8/2	61/25	36/15	140/60	64	2.4	670	270	1,560
2	28	F	1.43	Preop.	10/5	35/20	27/15	101/53	62	2.3	680	220	1,900
				14 days P. O.	6/1	32/12	10/6	109/60	64	3.0	337	131	1,430
				8 mo. P. O.	6/2	30/11	14/7	112/53	72	2.9	380	210	1,500
3	44	M	1.71	Preop.	17/5	88/43	49/11	143/78	70	2.6	925	360	1,465
				17 days P. O.	8/2	37/15	11/4	133/61	66	2.9	350	240	1,360
				8½ mo. P. O.	8/0	55/24	42/11	116/64	74	2.6	540	220	1,200
4	45	F	1.86	Preop.	9/3	56/25	30/11	156/89	68	2.3	618	290	1,890
				28 days P. O.	3/—3	24/6	8/4	111/54	63.9 ‡	3.1	170	102	1,060
5	46	F	1.50	Preop.	9/4	§	--	99/55	45	1.8	--	--	2,874
				P. O.	Not performed								
6	49	M	1.88	Preop.	10/1	76/39	28/16	117/86	48	1.6	1,160	685	2,190
				19 days P. O.	6/2	53/23	10/5	141/76	63.1	2.2	640	470	1,900
9	26	F	1.82	Preop.	9/4	52/26	39/14	117/54	67	2.6	595	220	1,225
				P. O.	Not performed								
11	35	M	1.72	Preop.	24/12	68/4 †	--	131/93	48	1.3	--	--	3,800
				10 days P. O.	8/3	58/23	22/13	117/67	66	4.0	490	200	1,005
12	31	F	1.47	Preop.	20/14	64/30	--	103/64	47	1.6	1,340	--	2,440
				P. O.	Not performed		¶						
13	26	M	1.99	Preop.	12/5	40/17	35/14	120/62	69	3.8	310	60	860
				12 days P. O.	8/4	31/12	14/7	100/55	72	3.4	210	105	860
14	47	F	1.57	Preop.	Not performed								
				14 days P. O.	8/4	49/23	11/7	118/69	56	3.7	430	308	1,130
15	42	M	1.90	Preop.	20/10	80/30	55/20	140/90	56	1.7	1,150	325	2,700
				17 Days P. O.	6/1	56/22	19/6	102/64	71	3.4	440	290	1,020

* No catheterization data available in cases 7, 8, and 10.

† Right ventricular pressure; repeated attempts to enter pulmonary artery unsuccessful.

‡ The low mixed venous blood oxygen saturation after operation is due in part to anemia (hemoglobin 10.5 gm. per 100 cc. of blood).

§ Repeated attempts to enter right ventricle unsuccessful.

¶ Wedge pressure not obtainable.

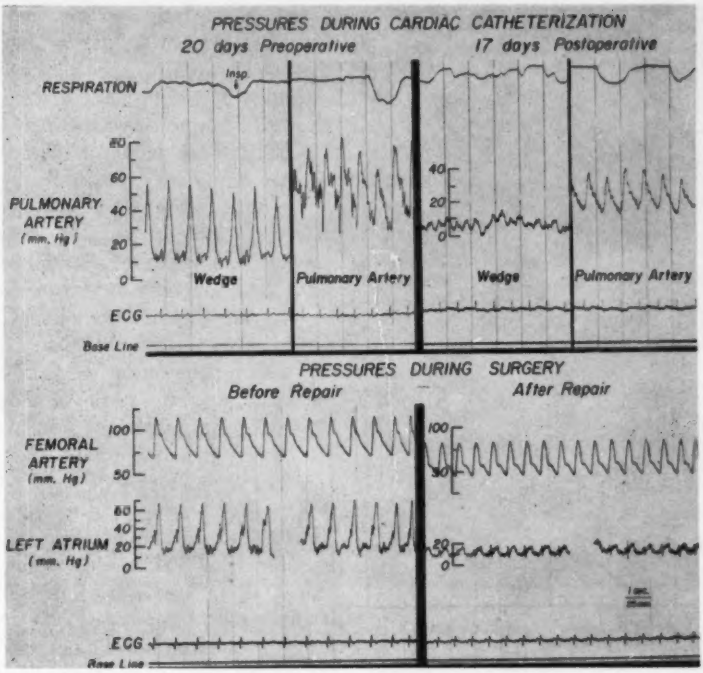


Fig. 2 (Case 3).—Intracardiac pressures before and after repair of mitral insufficiency in a 44-year-old man. In the upper panels are shown intracardiac pressures during the right-heart catheterization and in the lower panels during operation. Note (1) the tall, peaked V waves in the pulmonary-artery-wedge and left atrial pulse contours prior to operation and the normal wedge and left atrial pressures after annuloplasty, and (2) the reduction in pulmonary-artery pressure after operation.

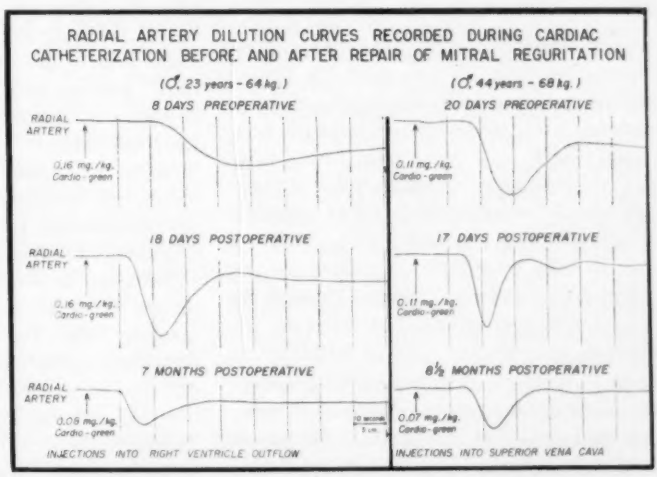

RADIAL ARTERY DILUTION CURVES RECORDED DURING CARDIAC CATHETERIZATION BEFORE AND AFTER REPAIR OF MITRAL REGURITATION
(♂, 23 years - 64 kg.)
(♂, 44 years - 68 kg.)
8 DAYS PREOPERATIVE
20 DAYS PREOPERATIVE
RADIAL ARTERY
0.16 mg./kg. Cardio-green
0.11 mg./kg. Cardio-green
18 DAYS POSTOPERATIVE
17 DAYS POSTOPERATIVE
RADIAL ARTERY
0.16 mg./kg. Cardio-green
0.11 mg./kg. Cardio-green
7 MONTHS POSTOPERATIVE
8½ MONTHS POSTOPERATIVE
RADIAL ARTERY
0.08 mg./kg. Cardio-green
0.07 mg./kg. Cardio-green
INJECTIONS INTO RIGHT VENTRICLE OUTFLOW
INJECTIONS INTO SUPERIOR VENA CAVA

Fig. 3.—Indicator-dilution curves recorded at the radial artery during right-heart catheterization before and after repair of mitral insufficiency in Case 1 (left panel) and Case 3 (right panel). The instant of injection of the indicator is shown by the vertical arrows. Note that the dilution curves recorded prior to operation show a decrease in the peak concentration of dye and disproportionate prolongation of the disappearance slope with absence of, or reduction in, the systemic recirculation peaks compatible with the diagnosis of severe mitral regurgitation. Immediately after operation the curves show marked improvement; however, there is evidence of regurgitation in both cases in studies carried out seven and eight and one-half months after operation, respectively. (Smaller doses of indicator were used in the late post-operative studies in both instances.)

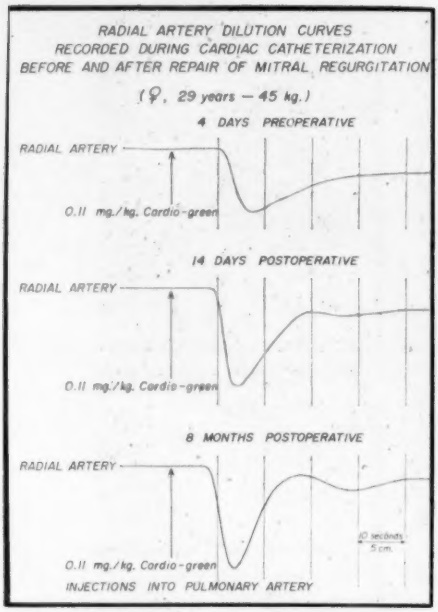


Fig. 4 (Case 2).—Indicator-dilution curves recorded at the radial artery during right-heart catheterization before and after mitral annuloplasty. The instant of injection of dye is shown by the vertical arrows. As in Figure 3, the curve recorded prior to mitral annuloplasty shows evidence of severe mitral regurgitation. Immediately following operation, the dilution curve shows marked improvement, but the disappearance slope is still somewhat prolonged. The contour of the dilution curve recorded eight months after mitral annuloplasty is normal.

cotomy incision through the bed of the nonresected fifth rib was used. A similar incision was used for three patients operated on later, one with constrictive pericarditis, one with associated aortic valve disease, and one in whom a ruptured papillary muscle was suspected and extracardiac tying of sutures was anticipated. Although this incision gives excellent exposure, we prefer an anterolateral incision through the bed of the nonresected fifth or sixth rib. Such an incision was used in 10 of the 15 cases. The costal cartilage of the proximal rib is detached from the sternum to facilitate exposure. For this incision the patient is semisupine; the right side of the thorax is elevated to an angle of 45 degrees. The advantages of this incision from the standpoint of prevention of air embolism have been pointed out by Cross and Thoms.[29] The pericardium is opened widely, and the heart is thoroughly exposed. Left atrial pressures are measured routinely before and after repair of the insufficiency. Cannulation of the venae cavae and a systemic artery, usually the right common femoral artery, is carried out and extracorporeal circulation is instituted. A modified Gibbon-type vertical-screen oxygenator is used to support the patient's circulation during the period of total cardiopulmonary bypass.[30]

Access to the mitral valve is usually obtained directly by an incision in the left atrium, as indicated in Figure 5, *a* and *b*. If the left atrium is small, adequate exposure of the valve may be obtained by opening the right atrium and incising the atrial septum. The latter approach was used in only 4 of the 15 cases. Asystole was employed in only one case in which aortic insufficiency was associated. A beating heart is essential for proper evaluation of the effectiveness of the operative procedure.

Findings.—Ruptured chordae tendineae were encountered five times. On three occasions the posterior leaflet was involved, and in two the anterior leaflet was affected. The involved leaflet in each instance was markedly elongated and everted freely into the left atrium during systole. A posterior leaflet which was retracted and deficient in tissue was a characteristic finding in most of the cases in which the chordae tendineae were not ruptured. Regurgitation frequently occurred throughout the extent of the valve, but usually it was more marked in the region of the posteromedial commissure. The anterior leaflet, although thickened and rolled along its leading edge, was uniformly pliable. Calcification was present in two instances only. Two patients had previously undergone mitral commissurotomy with incision of the posterior leaflet somewhat posterior to the true anterolateral commissure. Although the false incision was resutured in both, in only one did this reconstruction seem to reduce the insufficiency. In the other, annuloplasty was required to achieve

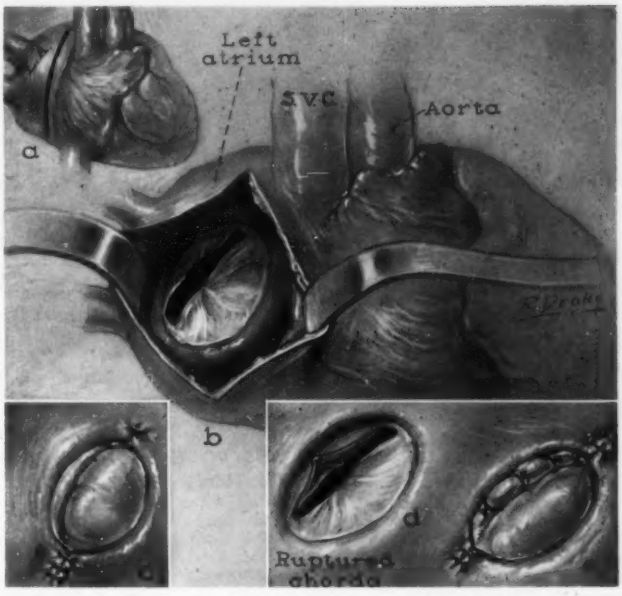


Fig. 5.—Technique of mitral annuloplasty. (*a*) A long incision is made in the enlarged left atrium anterior to the right pulmonary veins. (*b*) An unobstructed view of the annulus and valve leaflets is obtained. (*c*) The mitral orifice has narrowed in this instance by plication of the annulus over both commissures. (*d*) Rupture of the chordae tendineae of the posterior leaflet with eversion of the leaflet into the left atrium during ventricular systole. (*e*) The posterior leaflet has been converted into an immobile baffle by sutures placed through its free edge and through the annulus, thus enabling the normal septal leaflet to occlude the mitral orifice effectively after annuloplasty.

maximal reduction of mitral insufficiency. All but two of the patients were found to have relatively pure mitral insufficiency. In these two, however, commissurotomy was an essential part of the operative procedure, combined, of course, with measures designed to reduce the associated insufficiency. Although we had anticipated encountering a dilated mitral ring in all patients, it was present in only 9 of the 15.

Technique.—The technical aspects of the operative procedure must be individualized to the needs in the particular case. In the presence of a dilated ring, heavy through-and-through silk sutures are placed in the mitral annulus in the region of one or both commissures in order to narrow the mitral ring. These heavy silk sutures are reinforced by intervening sutures of lighter weight (Fig. 5, *c*). In the presence of a beating heart, increasing competence of the valve can be appreciated as properly placed sutures are snugged down. A full left ventricle is required for full appreciation of the competence of the valve, and it occasionally may be necessary to distort the aortic ring to allow regurgitating blood from the aorta to fill the left ventricle to capacity. Care, of course, must be taken to avoid producing a stenotic valvular orifice.

Ruptured chordae tendineae pose a serious technical problem, and two methods have been used in its correction. In three patients the flail, elongated, overshooting posterior leaflet was fixed to the left ventricular wall and mitral ring by multiple through-and-through silk sutures. Immobilized in this way, the posterior leaflet acts as a baffle which the anterior leaflet can meet during ventricular systole. It was also necessary to narrow the mitral ring in these cases (Fig. 5, *d* and *e*). Another method of correcting this condition, suggested by Dr. McGoon, consists of shortening the elongated portion of the leaflet, whose chordae have been ruptured, and tightening its leading edge by insertion of plicating sutures of 3-0 silk in a plane parallel to the leading edge of the valve (Fig. 6, *a* and *b*). In two cases this satisfactorily prevented eversion of the affected leaflet during systole and contributed to valvular competence. This method was used with partial success in another patient who had an overshooting

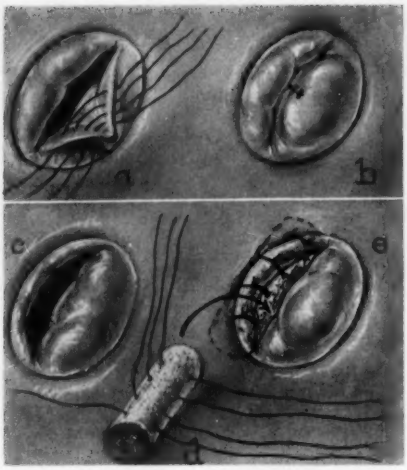


Fig. 6.—Operative technique. (*a*) Ruptured chordae tendineae of the anterior leaflet with plicating sutures in place. (*b*) Completed repair. (*c*) Deficient tissue of posterior leaflet without dilatation of the mitral ring. (*d*) Roll of compressed Ivalon. (*e*) Placement of Ivalon beneath deficient posterior leaflet.

anterior leaflet due to extreme laxity of the chordae tendineae.

In the absence of a dilated ring, when incompetence is due to deficiency of tissue in the posterior leaflet, proper positioning of a roll of polyvinyl formalinized sponge (Ivalon) can contribute to competence. The roll of Ivalon may be sculptured to suit the anatomic needs of the patient and sutured under the leading edge of the posterior leaf. In this way the deficiency of tissue is overcome and the anterior leaflet meets the newly placed prosthesis during systole and competence is achieved (Fig. 6, *c*, *d*, and *e*). This procedure was employed twice.

In two patients none of the previously mentioned maneuvers was effective in controlling the regurgitation.

Results

Clinical.—Two patients failed to survive the operative procedure and a third died on the ninth postoperative day with uncontrollable nodal tachycardia. Failure to relieve the mitral insufficiency undoubtedly contributed to the death of the last-mentioned patient, as well as one of those who failed to survive the operation. The other patient died of hemorrhage as a result of a suture cutting through the posterior wall of the left atrium.

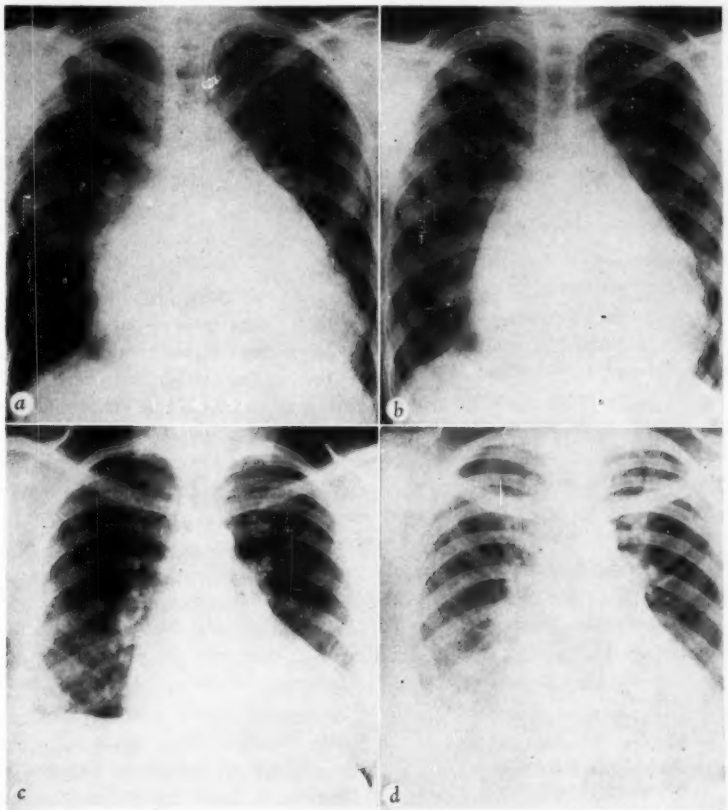
Complications were rare. A left hemothorax was evacuated postoperatively in one patient. Early in the series, before the dangers of air embolism were fully appreciated, two patients apparently suffered from this complication. Use of the right lateral approach and aspiration of air from the left ventricle and ascending aorta before discontinuing perfusion have prevented this complication in the remaining patients. The first patient operated on had three generalized convulsions over a two-day period beginning on the evening of the day after operation. The episodes were brief, and the patient had no immediate or late sequelae. Convulsions requiring intravenous diphenylhydantoin sodium (Dilantin) for control developed the morning after operation in another patient. She remained comatose for three days and then gradually recovered. Recovery has been complete except for slight weakness of the left arm and hand.

The postoperative course of the remaining patients was remarkably uneventful. It was smoother than for patients with equally severe disease due to mitral stenosis who have undergone mitral commissurotomy. At the time of dismissal, however, an apical murmur, graded 1 to 2, was commonly present; only two patients actually did not have a murmur. The murmur tended to be shorter than preoperatively and not widely transmitted. The significance of this residual murmur is not clear since it was not restricted to patients with hemodynamic evidence of residual insufficiency.

Postoperative evaluation of the effectiveness of the operation was possible in nine patients, three having been operated on too recently for evaluation. The follow-up period ranged from 3 to 12 months, averaging 7 months. Correspondence with the patient (one case), the physician (five cases), or

reexamination at the clinic (three cases) constituted the basis on which postoperative evaluation was made. One patient died rather suddenly in heart failure two months after operation; he apparently had done well until just before his death. A roll of compressed Ivalon had been used to substitute for deficient tissue in the posterior leaflet in this patient. Unfortunately necropsy was not obtained. Another patient (Case 5), who was bedridden before operation and whose roentgenograms are shown in Figure 1, *a* and *b*, continues to accumulate fluid and requires diuretics although she is considerably improved from her preoperative status. It is possible that further experience with such desperately ill patients will indicate a low salvage rate. The remaining seven patients are clinically well and have been classified functionally in Class I (N. Y. H. A.) as there appears to be no restrictions on what they can do. In these patients the clinical improvement has been gratifying. Of the three patients whose condition has been reevaluated at the clinic, two show some increase in the intensity of the apical systolic murmur. Late postoperative roentgenograms of the thorax have been reviewed in six patients up to eight months after operation. The cardiac silhouette has become smaller in four of them (Figs. 7 and 8). It was encouraging to note in one patient not only an initial decrease in the size of the heart but con-

Fig. 7. (*a* and *b*, Case 1).—Posteroanterior view. (*a*) Before operation. (*b*) Four months after operation. (*c* and *d*, Case 4) Posteroanterior view. (*c*) Before operation. (*d*) Three months after operation.



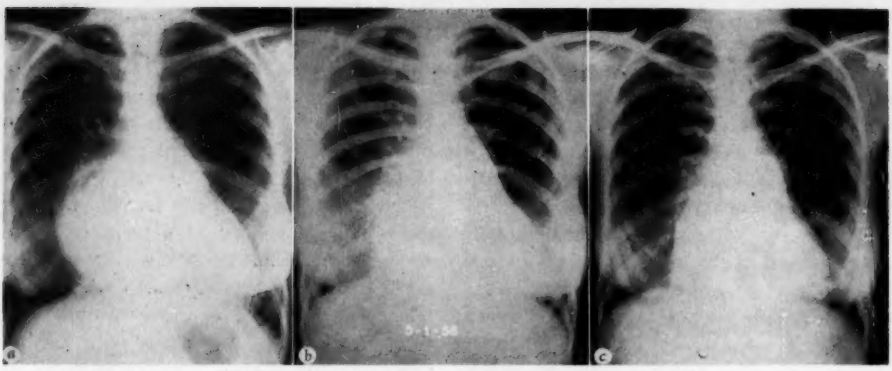


Fig. 8 (Case 2).—Posteroanterior views: (*a*) Before operation. (*b*) Two months after operation. (*c*) Four months after operation.

tinued decrease with the passage of time (Fig. 8).

Hemodynamic.—The recording of pressures in various heart chambers and great vessels during operation, combined with postoperative catheterization studies of the right side of the heart, affords objective evidence as to the efficacy of the intracardiac repair. Pressures in the left atrium and a systemic artery were recorded during operation, before, and in 13 cases after correction of mitral insufficiency (Table 3). The left atrial pressure in all except one of these cases (Case 5) decreased definitely after repair. Appropriate preoperative, postoperative, and operative pressure tracings from a representative case are presented in Figure 2. Table 2 summarizes the results of right heart catheterization before and after operation in these patients. There was a uniform decrease in the pulmonary-artery-wedge and pulmonary-artery pressures and in the pulmonary vascular resistance to normal or near normal values after operation. The cardiac index increased from below normal or low normal values preoperatively to normal values in the immediate postoperative period in all cases studied except Case 13. In this patient, who had no significant change in the preoperative and postoperative cardiac indexes, the preoperative cardiac index of 3.8 liters per minute per square meter of body surface was normal. The right atrial pressures, which were severely elevated prior to operation in five patients, decreased to normal values postoperatively in the four patients for whom data are available.

The use of indicator-dilution curves during right heart catheterization provides a

TABLE 3.—*Pressures Recorded at Operation Before and After Correction of Mitral Insufficiency* *

Case	Age, Yr.	Sex	Operation	Systemic Artery Pressure, Mm. Hg	Left Atrial Pressure, Mm. Hg
1	23	M	Before	103/51	48/16
			After	122/64	16/11
2	28	F	Before	104/59	51/15
			After	110/60	26/17
3	44	M	Before	114/68	68/14
			After	86/46	23/13
4	45	F	Before	116/68	48/25
			After	104/63	24/17
5	46	F	Before	92/58	32/18
			After	97/50	29/19
6	49	M	Before	104/80	55/10
			After	109/55	15/6
7	48	F	Before	82/54	52/24
			After	73/47	29/20
8	40	M	Before	110/90 †	35/25
			After	90/70 †	17 to 20 ‡
9	26	F	Before	126/55	67/25
			After	Not obtained	
10	52	M	Before	120/80 †	83/15
			After	120/80 †	14/8
11	35	F	Before	124/65	45/25
			After	113/64	26/19
13	26	M	Before	110/60 †	52/14
			After	100/80 †	16/10
14	47	F	Before	100/60 †	30/14
			After	120/50 †	21/11
15	42	M	Before	100/80 †	64/24
			After	110/80 †	29/9

*Operative pressures not obtained in Case 12.
† Pressures not recorded but obtained by cuff method.
‡ Oral report — no photographic record made.

good independent method of evaluating the degree of mitral insufficiency.[31] Typical examples of the indicator-dilution curves obtained before and after operation are shown in Figures 3 and 4. There was a dramatic improvement in the contour of the indicator-dilution curves at the initial postoperative catheterization in all instances. These findings correlate well with the symptomatic improvement experienced by most patients. Two of these patients (Cases 1 and 3), both of whom remain completely asymptomatic, have had a return of their pulmonary-artery or pulmonary-artery-wedge pressures to preoperative levels (Table 2) and their indicator-dilution curves, although more nearly normal than preoperatively, indicate the presence of some insufficiency of the mitral valve (Fig. 3). One of these patients (Case 1) was one of two patients who were found to have slight residual mitral insufficiency when the indicator-dilution curves were studied immediately after operation. In Case 3 the pulmonary-artery-wedge pressure and indicator-dilution curves were normal at the initial postoperative catheterization. However, two months after operation an apical systolic murmur had redeveloped. In a third patient (Case 2) no evidence of any hemodynamic abnormality was found when she was studied eight months after operation (Fig. 4 and Table 2).

Comment

These 15 patients represent for the most part examples of relatively pure mitral insufficiency. In only two was there any stenosis, and in these patients, although commissurotomy was required, mitral insufficiency was the predominant lesion. From a diagnostic standpoint, there are a few points worthy of note. All had loud pansystolic apical murmurs with wide transmission usually to the axilla. A systolic thrill was present in almost half of the patients. Although mitral stenosis was present in only two patients, a diastolic murmur was heard in 11. This murmur probably represents a flow murmur and should not necessarily be interpreted as indicating associated stenosis of the mitral valve. The absence of calcium on cardiac roentgenography was also characteristic of these cases.

The presence of ruptured chordae tendineae in a third of the patients was a surprising finding. Perhaps this is to be expected, however, in a group of cases selected purposely as examples of relatively pure mitral insufficiency. Although a dilated mitral ring was anticipated in every case, it was found in less than two-thirds of the patients. It is obvious, therefore, that mitral annuloplasty cannot serve as a routine technique but that the necessary technical steps will have to be individualized to the special needs of the case at hand. Although this paper is concerned only with acquired mitral insufficiency, it should be pointed out that a similar surgical attack on the insufficient mitral valve can be successfully performed when the lesion is congenital in nature and associated with an atrial or a ventricular septal defect.

Certain technical points bear repetition. The value of the right lateral approach, as far as both exposure and minimizing the risk of air embolus are concerned, seems well established. We believe that a beating heart is essential in the proper evaluation of the success of measures instituted to correct the insufficiency. A beating left ventricle which is full of blood helps greatly to demonstrate progressive competence of the valve as appropriate technical steps are taken. Associated aortic insufficiency, even if hemodynamically insignificant, can interfere seriously with the conduct of the operative procedure. In such instances the aorta may be clamped and ventricular contraction maintained by coronary artery perfusion during repair of the mitral valve. If necessary, repair of the insufficient aortic valve can be carried out concomitantly.

The immediate clinical response of patients with satisfactory repair is dramatic. This may be due in part to the fact that the left ventricle is suddenly relieved of its

extra load and immediately can function more efficiently. The early postoperative hemodynamic studies give graphic evidence of the effectiveness of the operative procedure. In all of the patients so studied, restoration of all physiologic variable studies to normal or near normal values occurred. Less encouraging is the fact that there was evidence in two of the three patients studied again after intervals of seven and eight and a half months of some recurrence of mitral insufficiency. Clinically, however, these patients have remained well. Obviously a longer follow-up period will be necessary before the long-term effectiveness of this operative procedure can be evaluated. The persistence of even a slight amount of regurgitation after repair again may set into motion the vicious cycle which eventually leads to more and more insufficiency. On the other hand, the operative procedure, although occasionally permitting the recurrence of some insufficiency, may prevent its progression to serious clinical manifestations. Obviously every effort must be made to eliminate the insufficiency completely, although we have not found this possible in every case.

The selection of patients for operation has yet to be clearly defined. Since these patients represent for the most part examples of relatively pure mitral insufficiency, little can be said concerning patients with a combination of mitral stenosis and insufficiency in whom calcification of the valve may be a prominent feature. At present we believe that patients with pure mitral insufficiency must have significant progressive functional disability before we advise operation. Since the procedure may prove to be palliative rather than curative and since in some instances it may permit a recurrence of the disease, a more liberal use of the operation is perhaps not justified as yet. We have not denied operation to desperately ill patients in chronic failure, although the risk may well prove to be high for such patients and the results less satisfactory than under more favorable conditions.

Summary

Fifteen patients have undergone open heart repair of acquired mitral insufficiency. Two also had moderate mitral stenosis, and five were found to have ruptured chordae tendineae. The tissue of the posterior leaflet was deficient in 10. The mitral ring was dilated in nine.

A right lateral approach without induction of cardiac arrest is preferred. A variety of techniques have been used, including mitral annuloplasty, plication of the elongated leaflet with ruptured chordae tendineae, and use of a compressed roll of Ivalon as a substitute for deficient posterior leaflet tissue.

There were three hospital deaths and one late death. Of the eight survivors operated on long enough ago for evaluation, seven have excellent functional results and one is improved.

The hemodynamic findings in nine patients studied by right heart catheterization soon after operation demonstrated in each instance normal or near normal values of all physiologic variables studied. Of three patients studied after a further interval of several months, two have shown evidence of some recurrence of mitral insufficiency.

Further time must elapse before this approach to the correction of acquired mitral insufficiency can be fully evaluated. At present we are advising open heart repair for patients with relatively pure mitral insufficiency when significant progressive functional disability is present.

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DISCUSSION

DR. DONALD B. EFFLER, Cleveland: It is an historic occasion when a discussant can get up and present a series a little larger than the one from the Mayo Clinic. [Laughter] We have taken 27 patients to surgery for the attempted correction of mitral insufficiency.

[Slide] In our earliest experience we used the conventional bilateral approach; this incision has been abandoned for open heart surgery in our institution. We now use the approach mentioned by Dr. Ellis—a right anterolateral thoracotomy with retrograde femoral cannulation.

[Slide] In addition to the routine cannulation we make a great point of cannulating the left atrium; the midcannula you see in the above diagram is an indwelling left atrial cannula. We believe that constant monitoring of the left atrial pressure, particularly if the heart gets into trouble, will be of great help, as it will prevent overdistention of the heart with retrograde damage into the pulmonary circuit.

[Slide] The approach to the mitral valve, as mentioned by Dr. Ellis, can be made directly through the left atrium; but we prefer to use the upper route which we think is more direct, namely, a transatrial approach going through the right atrium, making an incision in the atrial septum through the fossa ovalis.

It has been stated by persons who have actually had the unfortunate experience, that air embolus is a very real hazard in the direct approach to the mitral valve. To date this has not been a problem in our limited experience.

We believe that the position of the patient is extremely important, and if the left anterolateral approach, as mentioned by Dr. Ellis, is used, and particularly if one goes through the atrial septum as shown, air embolus is a rather remote hazard.

[Slide] This slide simply shows you the anatomical approach to the mitral valve using the transatrial route.

I think all of us who have attempted surgical correction of mitral insufficiency will agree that we have to be extremely careful when using the words "cured" and "corrected." Actually what we are trying to do is to offer a palliative approach, because most of these valves are hopelessly damaged, as Dr. Ellis said, and I believe it deserves considerable emphasis.

Frequently the key to the future is not what you do to the valve itself, but is in the patient's own myocardium. If the left ventricle has been destroyed by chronic failure, the patient may show little benefit (even if you get an appreciable drop in left atrial pressure).

Our experience has not been as favorable as the authors', and I am very much impressed when I see the tremendous drop in gradient that has been accomplished in most of the patients presented this morning. The small number of poor results represented here is probably related to selection. If you operate on a Class IV patient in ventricular failure, you will get poor results.

I am not as optimistic as Dr. Ellis from the standpoint of the patient who is desperately ill and who has to be taken to the operating room in failure. Our results have indicated that operation on the dying patient has more frequently resulted in death than anything else. So, we prefer to take the patient out of failure. If we can't accomplish this, we do not consider him a surgical candidate.

DR. ARTHUR VINEBERG, Montreal: I would like to tell you about seven cases of mitral insufficiency which have been operated upon by us at the Royal Victoria Hospital in the past 11 months. There have been two operative deaths. Five of these cases had been operated on previously, of whom two had slits made in the aortic leaflet toward the posteromedian commissure. Both of these patients have greatly benefited from a simple annuloplasty. These cases in our hands seem to have done very well.

Our first case was operated on in March, 1958, and in September, 1958, he showed a reduction in heart size of 4.2 cm. in the transverse diameter and 3.8 cm. in the posterior diameter. This was a case of pure mitral insufficiency with a five-finger opening in the valve and good leaflets. Twelve heavy silk sutures were placed in the annulus, starting at the posterolateral commissure so as to reduce the opening to a two-finger size. Of all seven patients there have been no cases of ruptured chordae tendineae.

We use the right anterolateral approach, entering the left atrium directly from the right side just as does Dr. Ellis, an approach which was first shown to me by Dr. Effler and apparently abandoned by him. When there is associated mitral stenosis with the insufficiency, a long-bladed forceps is passed through the valve and opened so as to keep the valve from trapping air in the left ventricle while we are working. When sutures are used to repair the annulus we use No. 2 braided silk going around the annulus, not through it as has been done by others when using a mattress suture. These sutures are then tied blindly in a small quantity of blood so as to reduce the

possibility of air entering the left ventricle. We think it important not to stop these hearts and only do so if there is very marked aortic insufficiency. We prefer to use powerful atrial suckers which return the bronchial pulmonary blood to the pump oxygenator. In the one patient in whom we had a completely destroyed aortic leaflet we used a rolled-up piece of Ivalon sponge to replace the absent leaflet. This man was on the extracorporeal circuit for two hours. Unfortunately, he died 12 hours after surgery from generalized hemorrhage. Apparently his entire clotting mechanism had been deranged so that the Christmas factor, etc., was missing.

I agree with Dr. Effler that if the cases are reasonably well selected and if there is still some reserve available in the left ventricle, this operation holds great hope for these patients who are otherwise disabled.

Dr. F. Henry Ellis, Jr., Rochester, Minn.: I would like to thank Dr. Effler and Dr. Vineberg for their remarks and to reemphasize some of the things that were brought out in the paper and by the discussants.

Dr. Effler's points regarding the palliative nature of this procedure are well taken, because we cannot as yet replace the mitral valve and transform this badly diseased mechanism into a normal one. All we can do is try to improve its function, admittedly in a less than perfect way.

The fact that two of our three patients who were recatheterized have shown some evidence of recurrence of mitral insufficiency is another indication that this is not a curative but a palliative procedure. Even though we are able to help patients symptomatically, we may not be able in every instance to bring them back to an entirely normal physiologic state.

You may have noticed that my remarks were confined primarily to pure mitral insufficiency. We cannot draw any conclusions regarding the combination of stenosis and insufficiency from the experience reported in the paper. Patients who have a markedly calcified valve that is not only insufficient but also stenotic pose a more difficult technical problem and the results may be less predictable. However, in a few recent cases with this combination of stenosis and insufficiency I was surprised at how much improvement in valvular function could be achieved by a plastic procedure on the valve.

The Relationship Between Right Atrial Pressure and Blood Volume

RICHARD E. HUGHES, M.D., and GEORGE J. MAGOVERN, M.D., Pittsburgh

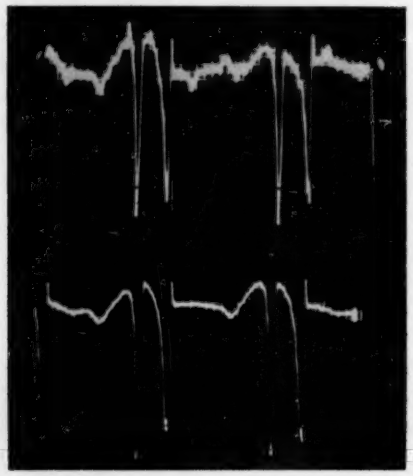
Introduction

Present clinical criteria for detecting alterations in blood volume in postoperative patients are inadequate. Laboratory studies to support suspected findings also leave much to be desired. Blood volume studies using radioactive substances and dilution techniques approximate most accurately the existing state at a particular unit of time but they do not determine the rate of replacement, rate of withdrawal, or effectiveness of such therapy except as judged by repeat blood volume or reevaluation and interpretation of clinical signs. It is the purpose of this study to determine the efficacy of continuous monitoring of right atrial pressure in the detection of blood volume changes as previously reported in the experimental animal.[1,2]

Methods

Twenty-five consecutive thoracotomy patients were studied with regard to their cardiovascular status, including frequent preoperative and postoperative blood volumes, measurement of hourly urine output, blood pressure, respirations, pulse rate, and clinical evaluation of each patient during the hospital course. The blood volumes were determined by using radioactive iodinated serum albumin and substituting a calibrated lead plug for the usual dilution techniques. Each patient had a PE 190 catheter inserted into the basilic vein on the day prior to surgery, except for eight of the patients who underwent open heart surgery utilizing cardiopulmonary bypass. In the latter patients, the catheter was inserted via the saphenous vein at the time of surgery and its position in the atrium determined by palpation. The position of the catheter early in the series was ascertained by the use of intra-atrial pressure recordings using a Statham P-23 strain gauge. In an attempt to simplify the localization and to eliminate the necessity of using special equipment, it was decided to position the catheter with intra-atrial electrical recordings, i. e., an intracardiac electrocardiogram. Accordingly the PE 190 catheter was filled with hypertonic 5% saline solution and the catheter introduced into the basilic vein and connected to the exploring lead of the electrocardiograph,[6] the other leads being connected to the patient in the usual manner. Immediately upon entering the right atrium the tracing assumes the contour depicted in Figure 1. It has been found that not only can cardiac chamber localization be determined by this method but also the level of the catheter tip within the particular chamber (Fig. 2). Positions of the catheters have been verified after injection of 70% sodium acetrizoate (Urokon) into the tubing by x-ray (Fig. 3). The catheter is then plugged and taped to the forearm and left undisturbed until after surgery.

Fig. 1.—Tracing of right atrial electrocardiogram.



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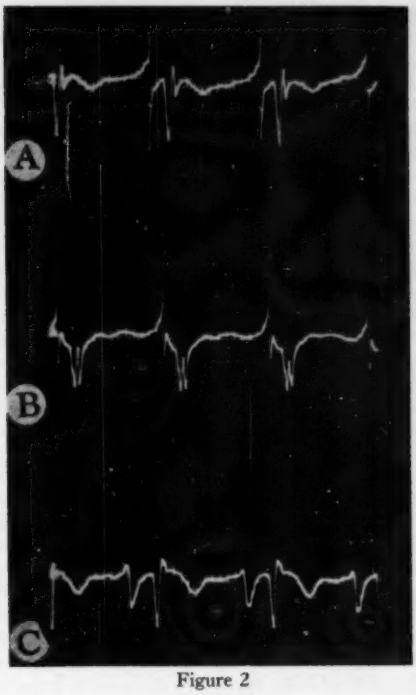

Figure 2

Figure 3

Fig. 2.—A, midatrial tracing. B, low atrial tracing. C, high atrial tracing.

Fig. 3.—Chest roentgenogram depicting right atrial catheter in position.

In the recovery room, the catheter is connected to a vertical piece of polyethylene tubing ¼ in. (0.64 cm.) in diameter and 30 cm. in length, which is labeled in 0.5 cm. increments above the zero level. Into this vertical tubing (manometer) is run a continuous drop of 5% dextrose in water containing 30 mg. of aqueous heparin per 500 cc. The rate of flow is adjusted to equal the absorption via the catheter (Fig. 4). The patient may change position without disturbing the manometer, and the atrial pressures are recorded in any position by the use of a level for obtaining the corrected zero mark. By using a constant rate of inflow via the infusion manometer, any change in right atrial pressure will be reflected by elevation or depression of the manometer fluid level. The catheter is left in place for 48 hours or longer postoperatively, depending upon the cardiovascular status of the patient.

Results

In 23 of 25 patients in this series, with replacement of known losses, the atrial pressures ranged from 2 cm. to 8 cm. of water with only slight variations in level in individual patients. There were no significant changes in blood pressure, pulse, hemoglobin, hematocrit, urine output, or blood volume, and thus the method correlated well with the atrial monitoring. In two of the

Fig. 4.—The continuous infusion manometer.

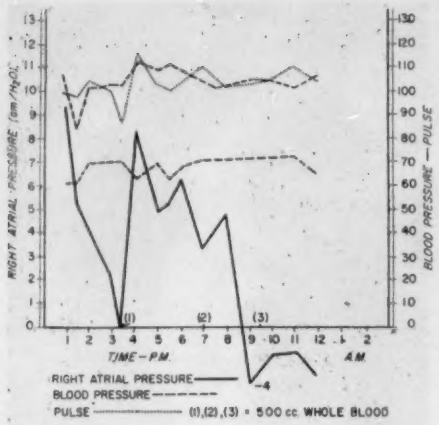

Fig. 5 (Case 14).—Right pneumonectomy.

cases, there were findings which illustrate the efficacy of the method.

Case 14 (Fig. 5).—A 56-year-old white man underwent left thoracotomy and pneumonectomy on Oct. 22, 1958, for carcinoma of the left main stem bronchus. His preoperative hemoglobin was 15.3 gm., and blood volume was 4,500 cc. with an estimated normal of 4,830 cc. The estimated blood loss at surgery was 1,200 cc., and he received 1,500 cc. before he left the operating room. Figure 5 depicts a graph of the patient's vital signs and atrial pressure recordings for the first 12 hours postoperatively. It will be noted that both systolic and diastolic pressures remain rather constant throughout this period. There is one significant elevation of pulse rate which occurred at 4:00 p. m. This was preceded by a bradycardia. The pulse otherwise remained constant. The atrial pressure, however, decreased from 9 cm. H_2O to 0 cm. H_2O in the space of one and one-half hours and preceded the tachycardia by approximately two hours. With the institution of blood replacement at 3:00 p. m., solely on the basis of right atrial pressure decrease, the right atrial pressure again became elevated. However, continued hypovolemia was evident from a further step-wise decrease over the next six hours. Hemoglobin and hematocrit of blood drawn at 4:00 p. m. indicated a 3 gm. drop over preoperative determinations. Blood volume for sample drawn the next morning indicated 4,400 cc. (a 100 cc. decrease over preoperative level), a hemoglobin of 10.7 gm. and hematocrit of 36%. During the first 40 hours postoperatively the patient required 24 units of whole blood, and replacement was performed on the basis of right atrial pressure determinations. During this period the systolic blood pressure ranged between 95 and 110 mm. Hg. The lowest hemoglobin and hematocrit readings were those recorded on the first postoperative morning. The blood volume on the second day postoperatively was 4,150 cc. (a 350 cc. deficit over preoperative level). Urine output was consistently above 500 cc. for 24 hours. The total chest drainage was 4,500 cc. and did not reflect the rate of blood loss or the total loss at any time.

Comment: Chest drainage, blood pressure, pulse, urine output, and the clinical appearance at no time reflected the rate or volume of whole blood loss in this patient. The atrial pressure decrease preceded by two hours the transient pulse elevation indicative of hypovolemia. The blood volume determinations merely reflected the adequacy of therapy at the time the test was performed. During the first postoperative day the patient received 1,500 cc. of whole blood in the course of five minutes, and the rate and amount of infusion were regulated solely on the basis of atrial pressure increase—not to exceed 15 cm. H_2O.

Case 17 (Fig. 6).—A 54-year-old white man underwent left thoracotomy, lysis of pleural adhesions, and biopsy of posterior mediastinal mass on Oct. 24, 1958. The preoperative blood pressure was 140/70, hemoglobin 14.3 gm., hematocrit 47.5%, blood volume 3,600 cc. The preoperative electrocardiogram was essentially normal. The blood loss at surgery was estimated at 1,000 cc., and this was replaced before he left the operating suite. He received 1,000 cc. of 5% dextrose in water in the first four hours in the recovery room. Approximately six hours postoperatively it was noted that he had an initial decrease in right atrial pressure to 5 cm. H_2O, followed in the next two hours by a rise to 14 cm. H_2O. An irregular rapid heart rate was noted almost simultaneously, together

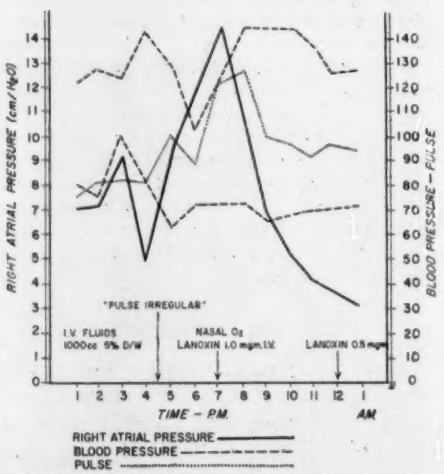

Fig. 6 (Case 17).—Left thoracotomy and biopsy.

with a fall in both systolic and diastolic blood pressures. The patient was obese, and peripheral venous distention was not a feature. The electrocardiogram indicated atrial fibrillation with a rate of 140. Hemoglobin and hematocrit determinations were 10.3 gm. and 38% respectively. Blood volume was not determined until the next morning. Nasal oxygen and Lanoxin (digitalis glycoside preparation) were given as the only treatment, with a well-correlated decrease in right atrial pressure and pulse, and a return of systolic blood pressure to normal level.

Comment: The postoperative hemoglobin and hematocrit decrease, the diminished blood pressure and elevated pulse as the only data available would tend to implicate hypovolemia as the predominant alteration in hemodynamics. However, the right atrial pressure monitoring disclosed a distinctly opposite trend, as proved by the therapeutic response to the measures instituted. It is postulated that the patient was hypovolemic as reflected by the hemoglobin and initial decrease in right atrial pressure, that this state precipitated myocardial anoxia, and triggered the atrial fibrillation. Thus, the secondary phenomena rendered the heart inadequate to handle further effective circulating blood volume without first correcting the arrhythmia and anoxia.

Comment

Blood Volume.—Measurement of blood volume by dilution methods is considered an excellent method of determining the status of the intravascular compartment, especially in the preoperative surgical patient who may have a chronic, compensated oligemia. It has also been used to determine the effectiveness of transfusions in the bleeding postoperative patient. There are many factors, however, which alter the effective circulating blood volume and which may be confusing in its interpretation: (1) the ability of the heart to handle the circulating blood, (2) the reliability of a single blood volume determination when blood is being lost and simultaneously replaced, (3) the problem of overtransfusion and precipitation of congestive failure, (4) the increasing error in repeated blood volumes in the same patient caused by the residual circulating radioactive material, and (5) the difficulty of adequate venipuncture on repeated occasions to inject all of the tracer material or dye into the vein.

Hemoglobin and Hematocrit.—These are both measurements of the concentration of red cell mass at the site from which blood is drawn per unit of time. It is of little value in the acutely bleeding patient or in the patient in congestive failure. It is of definite value as a base line, but depends on hemodilution to determine the degree of intravascular loss. This presumes the loss of whole blood only. In the case of hypovolemia secondary to loss of particular blood elements (e. g., burns, G. I. losses, etc.) further interpretation becomes necessary.

Blood Pressure and Pulse.—Pulse rate is a fairly accurate indication of suspected hypovolemia. However, the patient in congestive failure also manifests a tachycardia and, therefore, this cannot be used to differentiate the altered state of blood volume. Hypotension may also ensue with congestive states, further substantiating the erroneous impression of oligemia.

Urine Output.—As a reflection of oligemia, urine output is an excellent follow-up indicator of the degree of loss and adequacy of replacement of body fluids. However, there is necessarily a latent period coincident upon the production of urine, the transport to the bladder, and the all-important requirement of an indwelling Foley catheter.

Right Atrial Pressure.—It has been stated that central venous pressure is not an accurate index of blood volume. In the sense that it can give a quantitative expression of the number of circulating milliliters of blood, this is true. However, it does reflect accurately and instantaneously the functional pressure of the return venous flow as it enters the right heart, that is, it determines whether the compensatory mechanisms [4-8] which are brought into existence to restore and maintain hemodynamic equilibrium and maintain normal cardiac output are adequate. These mechanisms include selective arteriolar constriction, compression and emptying of venous volume reservoirs, increase in venous tone, elevation of pulse rate, and opening of arteriovenous shunts.

If these mechanisms are impaired or already maximally compensating a hypovolemia such as frequently occurs postoperatively owing to anesthesia or the results of a major surgical procedure, then the central venous pressure will initially reflect a decrease in the venous return and thus a loss of effectively circulating blood volume. If adequate blood replacement is then given, the necessary fall in the gradient at the ventricular diastolic level to maintain venous inflow will not occur; cardiac filling time will be maintained, and tachycardia and hypotension reflecting decreased cardiac output will not occur.

Indeed, as shown in Figure 6, in cardiac failure, whether it be due to intrinsic myocardial damage, arrhythmia, or absolute overloading of the vascular tree, hypotension and tachycardia may simulate blood loss. The central venous pressure, however, will rise, the only clinically reliable sign at this time indicating the true mechanism, and thus avoid further overloading of the vascular tree and compromise of the heart, until corrective measures are applied. Although an actual decrease in blood volume may be present, if the venous pressure is normal, the amount of blood present is all the heart can handle at that time and as such the continuous monitoring of the central venous pressure will reflect the effective circulating blood volume at any particular instant.

Since the failing heart dilates to maintain the cardiac output, the increased length of the fibers in diastole thus provides the proper systolic tension for outflow at this altered level of efficiency. At that point where the right heart can no longer handle the amount of blood being returned to it, there is an increase in the diastolic reserve volume, the heart failing to empty completely during systole. Thus very early changes in fiber length are reflected in right atrial pressure increments.

Right Atrial Pressure vs. Peripheral Venous Pressure: The right atrial pressure was selected here rather than peripheral venous pressure because the latter is subject to extramural pressures which give false indication as to the filling pressure of the right heart. Also, and perhaps more important, there is some element of constriction of venous channels at their point of entrance into the thoracic cavity. This would definitely tend to interdict a latent period in the reflection of atrial pressure changes. It is also felt that intermittent venous pressure readings would be of no more help than the occasional blood volume test by dilution methods. If atrial pressure recordings are to supersede the aforementioned presently accepted means of determining the cardiovascular status of the patient, then only the changes in this pressure as afforded by its continuous monitoring will give it its proper evaluation.

Summary and Conclusions

A method of localization of an intracardiac catheter is discussed, utilizing the intracardiac electrode with hypertonic saline as the conduction medium.

An attempt to correlate known methods of evaluating blood volume with right atrial pressure monitoring has been effected by the study of 25 postoperative patients undergoing thoracotomy.

It has been determined that right atrial pressure is an accurate and sensitive recording of the effective circulating blood volume.

It has been determined that right atrial pressure reflects changes in the cardiovascular system significantly in advance of the present methods of determining the status of this system.

It has been determined that adequacy and rate of treatment are accurately reflected by the right atrial pressure monitor, and two cases are presented to substantiate same.

It is suggested that this method be adopted for any patient in whom suspected alteration of hemodynamics may be considered of significant proportion.

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DISCUSSION

DR. GEORGE J. MAGOVERN, Pittsburgh: This study was an outgrowth of the use of continuous monitoring of venous pressure during extracorporeal circulation, wherein we use it as one of the parameters for determining the adequacy of perfusion.

At the conclusion of bypass the venous cannula is passed into the atrium and serves as a very reliable guide in determining whether the blood balance is adequate and whether or not the patient is handling the blood volume that is present in an adequate manner, so we can determine whether or not to perform decannulation.

As you know, once you do take out the caval cannula and give the protamine, you are not very prone to reinstitute bypass again. So, it is a very critical factor in our determinate state.

Within the past year we have used this on many more than the eight open cases that were described in this series.

We have actually used it on about 70 open heart cases.

Postoperatively, arrhythmia and blood loss in open heart surgery are common findings, and as such there is also a fair degree of peripheral vasoconstriction secondary to changes in pH. Although many investigators have stated that the atrial pressure is a late sign in determining blood volume, actually we have found that most patients, when they return from the operating room, either are maximally compensating, using the other methods to maintain a normal cardiac output, or else there are other mechanisms such as vasoconstriction that are depressed by anesthesia, and therefore the venous pressure is actually an early sign in determining the adequacy of the heart in maintaining output.

In this sense, then, the atrial pressure gives us an effective circulating blood volume determination. By this I mean that the blood volume actually may be lower than the preoperative blood volume, but the heart (because of the surgery) is able to handle what it has, and any further blood at this time would be hazardous. In that sense, if the venous pressure is normal, then we do not give more blood.

Other uses are helpful, as illustrated in the presentation, in determining whether or not congestive failure is present or whether hypotension is on the basis of inadequate blood replacement. It also serves as an avenue for administration of various drugs and blood; and also, inadvertently many times, since it is in the atrium after an atrial septal defect repair, it is a very convenient method to get a sample so that you can determine whether an oxygen step-up is present, and therefore you can tell early whether you have adequately closed the defect.

Recently we operated on a 21-year-old man with an ostium primum who for nine hours postoperatively did well and then had a drop in venous pressure from 7 to 2. His blood replacement was carried out solely on the basis of venous pressure. He was taken to the operating room after 7 units of blood were given, and was found to be bleeding from an internal mammary artery, and subsequently did well.

DR. RICHARD HUGHES, Pittsburgh: I believe this procedure can be utilized very well in seriously ill, general surgical patients as well as in those undergoing open heart surgery.

Deceleration Injuries of the Thoracic Aorta

KIRK CAMMACK, M.D., Boise, Idaho; RICHARD L. RAPPORT, M.D.; JOSEPH PAUL, M.D., and W. CLAIRE BAIRD, M.D., Flint, Mich.

Traumatic rupture of the thoracic aorta is an injury which should respond favorably to surgical repair if vascular continuity can be reestablished. In Hurley Hospital during the past six years, however, all nine patients seen with this injury have died. Three of these might have been saved if the correct diagnosis had been made and aggressive surgery carried out. Six more died shortly after entering the hospital but presented typical aortic lacerations that will aid in analyzing the characteristics of the injury.

With the advent of rapid transportation, reports of closed ruptures of the aorta have increased. An excellent summary of the cases previously reported has been presented by Strassmann [1] and more recently by Eiseman.[2] Reported repairs of chronic traumatic aneurysms produced by incomplete lacerations of the aorta are not uncommon.[2-6] The diagnostic radiographic signs have been presented by Wyman.[7] Numerous studies by the Air Force on the effects of sudden deceleration have indicated that lacerations of the heart and great vessels are commonly seen at autopsy.[8-10] The mechanical factors concerned in the production of closed ruptures of the aorta have been outlined inadequately.[1,11,12] We are not aware that this injury has been experimentally reproduced, although Lloyd has ruptured major bronchi in dogs with an impact type load and encountered several instances of lacerations of the aorta as well as of the myocardium.[13,14] His experimental method was such, however, that true deceleration was not simulated. Repair of acute lacerations of the thoracic aorta has been reported only in patients who suffered penetrating wounds of the chest which prompted early thoracotomy.[15-17] *

Accidents causing closed ruptures of the aorta may be separated into three groups: (1) those associated with direct crushing forces, (2) vertical, and (3) horizontal deceleration injuries.

Crushing forces usually cause multiple injuries, so that the torn aorta becomes only one of many findings elicited at autopsy.

Vertical deceleration injuries are usually associated with jumps from great heights or elevator falls. When a person is decelerated suddenly from the upright position, the freely suspended heart continues to travel earthward until it is abruptly restrained by its attachments to the great vessels, principally the aorta. Maximum stress is transmitted from the aortic origin distally. In such injuries the aortic tear usually occurs immediately above the aortic valve. Associated injuries are usually so severe that repair is not practical. The one patient in our series who suffered this type of vertical deceleration died instantly, and multiple injuries were demonstrated at autopsy.

The patient with traumatic rupture of the aorta who is most amenable to surgical correction is injured by horizontal deceleration.

Illustrative Cases

Eight instances of closed rupture of the aorta produced by horizontal deceleration

Submitted for publication Feb. 27, 1959.

From the Section for the Surgery of Trauma (Thoracic Surgery), Hurley Hospital.

Read at the 16th Annual Meeting of the Central Surgical Association, Montreal, Feb. 20, 1959.

* Since preparation of this manuscript we have been advised by Dr. Karl Klassen of Columbus, Ohio, that he has made the preoperative diagnosis and successfully repaired a closed deceleration laceration of the aorta eight hours after trauma.[14]

TABLE 1.—*Cases of Deceleration Injury to the Thoracic Aorta*

Patient	Age	Length of Life	Comments
1	43	6 hours	Thoracotomy for cardiac arrest; rupture not detected at operation
2	30	14 days	Complete transection below arch; 5 cm. separation of transected ends
3	42	6 days	2.5 cm. laceration base of aorta
4	66	2 hours	Rupture at base
5	64	D. O. A.	Rupture at distal arch
6	55	D. O. A.	Rupture at base
7	60	D. O. A.	Rupture at distal arch
8	30	D. O. A.	Rupture at distal arch
9	74	1½ hours	Rupture at base into right ventricle, unsuccessful thoracotomy

represent the problem with which this communication is concerned.

The first patient (Patient 1) developed cardiac arrest during an operative procedure for bilateral fractures of the tibia and ruptured abdominal viscera caused by an automobile accident (Table 1). When thoracotomy was performed for cardiac resuscitation, hemorrhage was noted about the aorta and posterior mediastinum, although no active bleeding was encountered. Five hundred cubic centimeters of blood was present in the pleural cavity. The patient survived cardiac resuscitation, only to die two hours later. At autopsy, complete transverse rupture of the aorta 1 cm. below the arch was demonstrated (Fig. 1).

A second patient (Patient 2) also could have been salvaged if the correct diagnosis had been made and aggressive surgery done early. This was a 30-year-old woman admitted to the

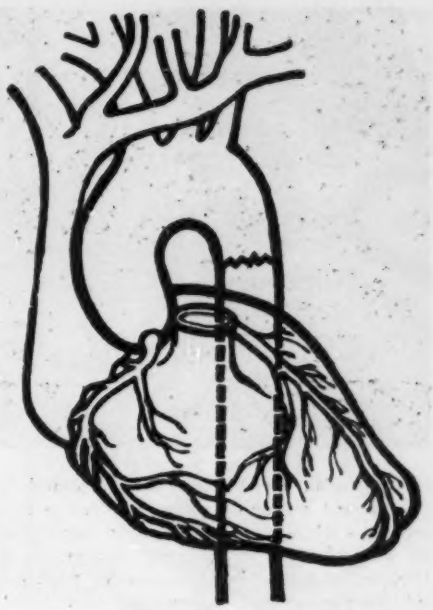

Fig. 1 (Patient 1).—Site of laceration.

Emergency Receiving Department with multiple lacerations, moderate head and chest injuries, and an intertrochanteric hip fracture (Table 1). Her shock was out of proportion to the obvious trauma present, but she responded well to whole blood transfusions. Skeletal traction was applied to the fractured femur and treatment was initiated for the head and chest injuries. Her general condition improved over the next seven days, and definitive surgery for the fractured hip was considered.

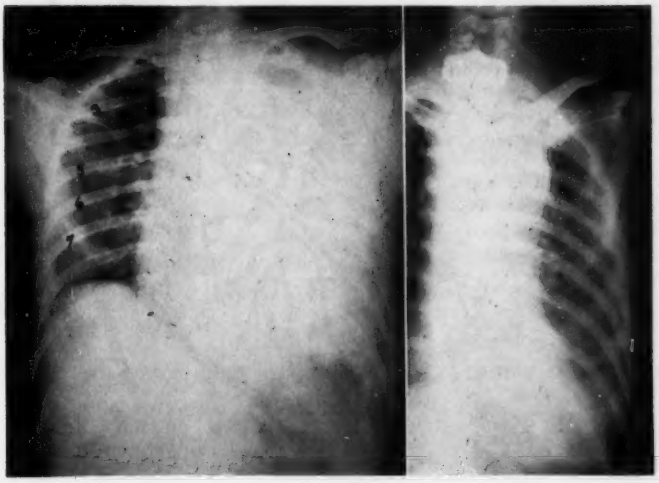

Fig. 2. (Patient 2).—Left, chest x-ray on eighth day after trauma, indicating left hemothorax and widened mediastinum. Right, chest x-ray after thoracentesis and tracheostomy. Note characteristic widening of mediastinum.

Fig. 3 (Patient 2).—Autopsy findings. Note 5 cm. separation between transected ends of aorta.

On the eighth day, however, she complained of dyspnea and abdominal distention. Chest x-rays revealed a left hemothorax with some widening of the mediastinum (Fig. 2). After thoracentesis of 1,000 cc. of bloody fluid, considerable subjective and roentgenographic improvement was noted. After several hours, however, she again complained of dyspnea and rapid, stertorous breathing. Ecchymoses appeared in the neck. Tracheostomy was done, and old blood was encountered. A thoracic surgical consultation was then requested. Chest x-rays taken at that time indicated a widening of the superior mediastinum on the left (Fig. 2). Considerable difficulty was encountered in keeping the respiratory tract free of secretions despite the tracheostomy. When shock, dyspnea, cyanosis, and semicoma became evident, an anterior mediastinotomy was elected. Blunt dissection with the finger beneath the sternum revealed a baseball-sized mass palpable to the left over the aortic arch. Pulsation was felt, although this was erroneously thought to be transmitted. Because of the patient's moribund condition, drainage only was elected. She died 14 days after admission to the hospital. Autopsy revealed a large, thin-walled aneurysmal sac 1 cm. below the distal aortic arch. On examination of the aorta complete transection was seen with a separation of 5 cm. between the transected ends (Fig. 3). Continuity of the blood stream was maintained only by the adventitia, which was dilated to a width of 10 cm. There was no evidence on gross or microscopic examination of aortic pathology except for the traumatic rupture.

Another patient (Patient 3) entered with an admitting diagnosis of multiple contusions and abrasions only (Table 1). Four days later she complained of substernal discomfort with radiation down her left arm and shortness of breath. There was no evidence of hypotension or hydrothorax. She suddenly died while straining at stool on her sixth post-trauma day. Autopsy revealed an irregular rent, 2.5 cm. long, completely through the base of the aorta, which opened into a saccular space 4 cm. in width (Fig. 4). Rupture into the pleural space had caused her death.

Five other patients injured in deceleration accidents were either dead on arrival or died shortly after entering the hospital without definitive therapy (Table 1). They all presented massive total body trauma and aortic lacerations typical

Fig. 4 (Patient 3).—Autopsy findings. Laceration through base of aorta opening into aneurysm.

of deceleration injuries to the aorta. Two lacerations were at the base of the aorta and three at the distal arch. Their average age was 55.

Mechanism of the Injury

Experience indicates that there are two principal sites for traumatic rupture of the aorta: (1) at the base of the heart, and (2) immediately beyond the arch of the aorta. Many occur without evidence of gross injury to the bony thorax. When the problem is examined from an engineering point of view, several factors present themselves for consideration. The bony thorax and the vertebrae which support the vascular structures comprise a framework which is a flexible column when under the influence of an impact type of load. Experiments have indicated that the thoracic cavity can be so compressed that the sternum is in contact with the vertebrae.[9,10,13] This sets an upper limit to the range of motion of structures within the thorax. The ribs will be deformed in a rather complicated pattern, and, since they are not an independent system, they will undergo a change of position during the period of deceleration. The deformation will contain a damped oscillation. The stresses produced in any rigid body due to an impact load will depend upon the elasticity of the material. Higher stresses are produced by impact loads than by gradually increasing loads having the same deformation.

During the time of deceleration, when the chest wall is changing shape, the aorta is undergoing similar stresses. Since it is considerably less elastic than the rib cage it will undergo greater changes in shape and, therefore, greater differential changes in stress. (The elastic limit is the maximum unit stress to which a material may be subjected and still return to its original form upon removal of the stress. Thus, a steel bar is more elastic than a rubber band.)

If we place as an upper limit of the compressibility of the AP diameter of the chest a dimension equal to the distance from the sternum to the vertebrae, then the heart and mediastinal structures will be displaced

Fig. 5.—Diagrammatic representation of displacement mechanism and forces involved in deceleration injuries of the aorta.

into the left chest posteriorly and the aorta rotated, producing a more tortuous course [13] (Fig. 5). There are three stresses involved in such a procedure: a *torsion* stress, which in tangential to the surface; a *shearing* stress, which is roughly in a radial direction, and a *bending* stress, which lies along the long axis of the aorta (Fig. 5). Since the aorta is a very inelastic structure, the bending stress can be entirely neglected. The torsion stress, which is a function of the deformity of the aorta produced in the deceleration procedure, and the shearing stress, which is due principally to the pressure wave associated with the impact, are the two principal components to be considered. In almost all reported cases, the tear in the aorta has been circumferential rather than linear (Fig. 6). This further substantiates the fact that the forces involved combine torsion and shearing.

The greatest change in the anatomical relationship of the aorta and the heart

Fig. 6.—Diagram illustrating characteristic locations and circumferential nature of the tear in deceleration injuries of the aorta.

occurs at the base of the heart and in this region the torsion stresses are greatest. On the other hand, ruptures which occur in the descending portion of the aorta are in an area where the shearing stresses predominate. This is due to a traveling pressure wave as well as to the fact that the aorta is fixed in this area by the ligamentum arteriosum and by its attachments to the chest wall.

Two cars moving towards each other at 60 miles per hour would collide at 120 miles per hour, or 176 ft. per second. Studies have indicated that deceleration of this impact type occur within 0.1 to 0.2 second. It is possible to estimate the range of motion during such impact time. If we neglect the minimal deformity of the steering column and assume that all deformity occurs in the compression of the thoracic cage, a compression of the chest wall of 10 cm. to 30 cm. will result. Using a simple relationship of distance, time and acceleration, as expressed in the formula $S = UT + 1/2\ AT^2$ (S equals displacement; U equals initial velocity; T equals time, and A equals acceleration), we arrive at decelerations which range from 300 ft. per second per second to 2,400 ft. per second per second. Expressed in the force of gravity, this figure is 10 to 80 g. If we assume that the great vessels in the heart are filled with blood at the time of impact and the weight of the heart is approximately 350 gm., a deceleration of 80 g will produce a pressure of at least 24 lb. per square inch, or 1,250 mm. of mercury. Klolz and Simpson have shown that a healthy aorta can be ruptured if pressures are greater than 1,000 mm. of mercury.[18] Oppenheim required pressures as high as 2,070 mm. of mercury to rupture the aorta.[19] These refer to static pressures rather than to an impact type load as seen in the production of a ruptured aorta. Owing to the nature of the force, much greater stresses are created by the latter mechanism.

Pressures produced by compression of the heart will be transmitted through a relatively incompressible fluid, the blood, and a relatively inelastic wall, the aorta. We can thus set approximate limits of stress. The strain can be determined only from experimental studies using static relationships such as are used in elasticity problems of structural engineering. The modulus of elasticity (the ratio of stress to strain per unit area) is probably of very low value, but accurate data are not now available. We know from studies of thin-walled materials that maximum stresses occur at the inner surface and are a direct function of the internal pressure and the ratio of the inner and outer radii of the pipe.[20,21] We also know that the breakdown of the elastic action of the material subjected to a combination of stresses begins only when the maximum shearing stress reaches the shearing proportional limit of the material.[20,21] Information concerning the shearing proportional limit of the aorta is not available from physiologic studies. The normal aorta is designed to handle internal pressures but is not designed to resist bending or torsion. The bending stresses are of minimal impor-

tance because of the thickness of the wall, but the stresses produced because of the torsion of the aorta at the time of compression are extremely important.

The mechanical principles involved in acute rupture of the aorta may be summarized as follows:

1. A sudden impact load can induce stresses which are considerably higher than a gradually increasing load.

2. As deceleration takes place, the heart is displaced into the left chest and posteriorly, either by compression of the chest wall or by deceleration per se. This produces (*a*) torsion stress (tangential); (*b*) shearing stress (radial). The torsion stress produces a pressure wave of blood that is transmitted through the aorta. A maximum internal pressure is produced at the point of greatest fixation of the aorta to the chest wall (immediately distal to the ligamentum arteriosum) which produces concentrated shearing stresses in this area.

3. The maximum stress occurs at the inner surface of the vessel, and the tear occurs from the intima towards the adventitia. The adventitia, having a lower elastic limit, often withstands the stress. This accounts for aneurysms often seen following aortic lacerations.

Comment

Analysis of the cases presented has helped reconstruct a clinical picture of the patient likely to have a deceleration laceration of the aorta. The following syndrome should alert the surgeon to consider the diagnosis: (1) history of deceleration injury; (2) shock out of proportion to obvious trauma; (3) dyspnea and chest pain; (4) hemothorax, usually left, and (5) chest x-ray showing a widened mediastinum (Table 2). If these signs and symptoms are kept in mind, diagnosis of acute rupture of the aorta will be made and early thoracotomy might be lifesaving. Others have suggested that thoracotomy is done too seldom in penetrating wounds of the chest.[22] We agree with this view and, indeed, believe that too few severe closed chest injuries receive the benefits of early thoracotomy. Since the diagnosis of lacerated aorta is difficult to establish clinically, this is another urgent reason to consider early exploration of the severely injured chest.

TABLE 2.—*Signs and Symptoms of Deceleration Injuries of the Aorta*

1. History of deceleration injury
2. Shock, out of proportion to obvious trauma
3. Dyspnea and chest pain
4. Hemothorax, usually left
5. Chest x-ray indicating widened mediastinum

If periaortic ecchymosis is seen at thoracotomy, a thorough inspection of the aorta at the usual sites of rupture should be carried out. A completely transected aorta may be obscured by ecchymotic adventitia and a potentially reparable lesion missed. Eiseman has reported a case similar to one of ours and even recommends exploratory aortotomy if the surgeon is suspicious of a ruptured aorta.[2] Our second patient was able to survive 14 days with a complete transection of the descending aorta so that only the adventitia directed the blood in its course. Since the adventitia accounts for 60% of the strength of the aorta, it can be readily understood how chronic traumatic aneurysmal dilatation of the aorta can occur.

Surgery would probably not have benefited the third patient discussed because of extension of the laceration into the myocardium and the sudden massive hemorrhage which occurred.

Study of our previous cases had placed us on the alert for a patient with a ruptured aorta who might benefit by early diagnosis and surgery. Our most recent patient was a 74-year-old man (Patient 9) admitted to Hurley Hospital after a deceleration injury with evidence of fractured ribs and multiple contusions and abrasions (Table 1). His blood pressure on admission was 100/70. X-rays revealed fractured ribs and a hydrothorax on the right. The patient appeared not severely injured until he suddenly developed shock out of proportion to his injuries. There were no breath sounds on the right side. The abdomen was negative. There were no major fractures of the extremities. He was taken to surgery with the diagnosis of possible ruptured aorta,

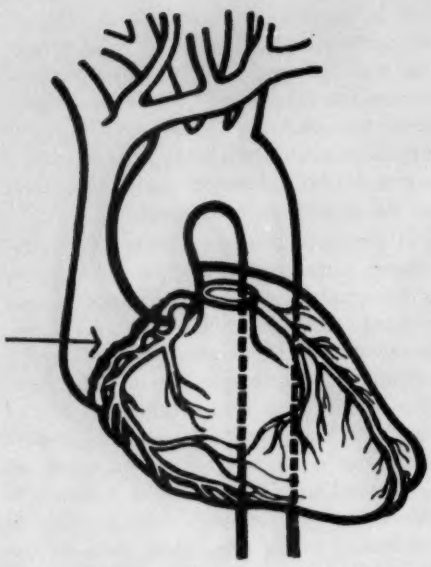

Fig. 7 (Patient 9).—Diagram illustrating site of laceration. Rupture of the aorta at its base with extension into the right auricle.

and exploratory thoracotomy was performed. The arch of the aorta was normal, but there was cardiac tamponade with rupture of the aorta at its base also involving the right auricle (Fig. 7). An attempt was made to repair both injuries, but he died on the table. If the tear had been in the descending aorta, as 50% of them are, we might have been able to report successful management of this case.

We are disappointed in our results, but not discouraged. Our experience has reinforced our thinking that early thoracotomy is the treatment of choice for severe injuries of the chest.

Summary

An attempt has been made to explain the forces concerned in deceleration injuries of the thoracic aorta and to account for the usual sites of laceration on a physical basis.

We have stated the signs and symptoms of this injury and have urged early thoracotomy when any consideration has been given to such a diagnosis.

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The Kidneys in Surgery of the Abdominal Aorta

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The kidneys are organs of singular significance for the surgeon operating on the abdominal aorta. Their anatomic disposition often creates grave technical problems and their functional state has intimate relationship to diagnostic studies, case selection, and operative results. In this essay, we wish to illustrate, with a background experience of 250 cases of abdominal aortic operations, the more important of these problems and to discuss, respectively, their recognition, prevention, and management.

Problems of Renal Physiology

The candidates for surgical procedures on the abdominal aorta are almost always suffering from systemic arteriosclerosis, often to a severe degree. As one of the commonest organ manifestations of this disease they often have some measure of renal arteriosclerotic involvement. While this fact is not always demonstrable by clinical tests, it is well borne out by operative and postmortem observations. It is not only prudent but physiologically correct, therefore, to regard every patient with arteriosclerotic disease of the abdominal aorta severe enough to require surgical treatment as having a reduced renal reserve, or perhaps more precisely, as having a diminished ability to withstand the physiologic assault of a surgical operation of great magnitude. This circumstance adds special significance to the considerations that follow.

Aside from the elusive injuries of operative trauma, the kidneys may be subjected to direct physical damage in two principal ways peculiar to aortic surgery: through ischemia due to occlusion of the abdominal aorta by clamping and through chemical trauma inflicted through the injection of contrast media in the course of diagnostic studies.

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From the Department of Surgery, Henry Ford Hospital.

Read at the 16th Annual Meeting of the Central Surgical Association, Montreal, Feb. 20, 1959.

The Effect of Occlusive Clamping of the Aorta

The ischemic effect on the kidneys of the clamping of the aorta proximal to the renal arteries is easy to see. A similar effect when the clamp is placed close to the renal arteries but distal to them is less obvious and more difficult to prove.

Suprarenal Clamping of the Aorta.—The clamping of the aorta proximal to the renal arteries may become necessary in three circumstances. The most frequently encountered situation demanding this technical step in our experience has been that seen in aortoiliac occlusive disease when the obliteration of the aorta extends to the immediate distal neighborhood of the origin of the renal arteries. In such an event the safest technical procedure for clearing the aorta of obstruction demands the clamping of the renal arteries individually either with or without simultaneous clamping of the suprarenal aorta (Fig. 1). If the renal arteries are not handled in this manner, the extraction of the thickened aortic intima and of thrombi may easily force debris into the renal arteries with the most serious possible consequences. Fortunately the entire maneuver requires only a few minutes, certainly less than 10 minutes.

Another circumstance requiring the placing of an occlusive clamp on the aorta above the renal arteries is presented by an aneurysm that either extends above the renal arteries or comes to an end directly distal to them. The former condition is quite rare, occurring only in about 10% of all true

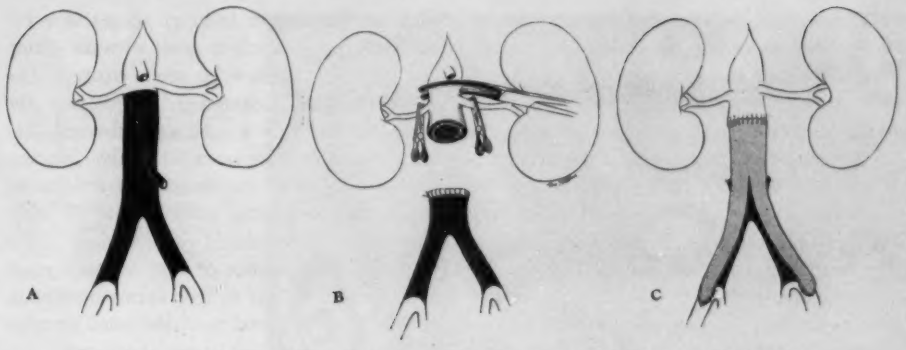

Fig. 1.—A commonly encountered lesion requiring cross clamping of the aorta above the renal arteries. (*a*) Aortoiliac occlusive disease extending to the immediate vicinity of the renal arteries. (*b*) In order to remove the occlusive substance (atheromatous intima and clots) from the aortic lumen without the danger of forcing debris into the renal arteries, the aorta and the renal arteries are clamped in the manner indicated. Once the thromboendarteriectomy is completed, the clamps on the renal arteries are removed, and the aortic clamp is transposed to an infrarenal position. The 10-15 minutes' occlusion time necessary for the maneuver is well tolerated. The prosthetic replacement is then carried out in the desired fashion (*c*).

abdominal aortic aneurysms. (Involvement of the renal arteries in low thoracic aortic aneurysms is somewhat commoner but its discussion does not form a part of the present writing.) Aneurysms that reach to the very level of the renal arteries, on the other hand, without actually encroaching on them are fairly common.

A not uncommon need for occlusive clamping of the aorta above the renal arteries arises in dealing with ruptured aneurysms. When the aneurysm is large and extravasation of blood extensive, the repair of such lesions is best started by clamping the abdominal aorta above the celiac axis after access has been gained through the gastrohepatic ligament and posterior parietal peritoneum. A relatively bloodless field is thus obtained in which the exact disposition of the aneurysmal sac with the point of rupture can be ascertained, the clots quickly removed, and the infrarenal aortic stem identified. Once the latter is accomplished the clamp is removed to an infrarenal position and the resection of the aneurysm carried out.

The method one chooses to avoid or minimize the effect of the ischemia brought about by aortic clamping depends on the facts of the individual case but is ultimately determined by the predictable tolerance of the kidneys to the lack of blood inflow. The upper limit of the safe period of inflow stoppage for the average healthy human kidney has not been exactly established. Our own observations in eight instances of occlusive clamping of the suprarenal aorta have definitely disclosed that a kidney without clinically manifest disease tolerates well complete stoppage of inflow for 30 minutes. Past this period of time the danger of serious damage is great, although we observed one case in which complete renal ischemia for 52 minutes resulted in only temporary oliguria with complete restoration of function in 8 days.

In light of this information, the temporary ischemia from clamping the renal arteries in the management of occlusive disease as outlined above obviously requires no special precautionary measures. The brief period of inflow stoppage (10-15 minutes) is withstood without consequences. Conditions are quite similar in the case of a ruptured aneurysm requiring clamping of the suprarenal aorta. Here, however, speed must be applied to clearing the field for the transposition of the clamp into an infrarenal location within the allotted 30 minutes. If

this time limit is exceeded before completion of the necessary dissection, it is advisable to release the high aortic clamp for a few seconds even at the expense of some blood loss (which by judicious packing can be greatly lessened). When the renal arteries are clearly encroached on by the aneurysm, that is, when one artery or both arteries take their origin from the wall of the aneurysm, complete reliance on the 30-minute safe period in planning the operative procedure is not always safe. It is usually feasible to make the aorta-to-graft anastomosis and to reunite one renal artery to the graft within this time limit, but a triple anastomosis (aorta to graft and two renal arteries to graft) within 30 minutes would in most hands be impossible. When, in addition to the renal arteries, the superior mesenteric and celiac arterial trunks also must be reimplanted, the available safe time is clearly insufficient. In the latter instances (that is, in cases requiring two renal and one or more additional visceral anastomoses) special techniques utilizing a pump or temporary shunt are necessary, the details of which are beyond the scope of this discussion. The total occlusion time of the aorta when a triple anastomosis is needed may also be reduced by anastomosing, as a first step, the left renal to the splenic artery.

The handling of the problem posed by the aneurysm flush or almost flush with the renal arteries presents a tantalizing dilemma. In most of these cases there is a very narrow brim of aorta directly distal to the renal arteries, the width of which, however, is insufficient to receive both the clamp and the suture line. One's instinctive reaction to this set of relationships is to convince oneself that the most proximal portion of the aneurysm is really not so badly decayed as to be unsuitable for accommodating the suture line. One then uses this marginal material for the affixation of the graft, taking a considerable chance on the development of a later aneurysmal dilatation proximally. A sounder method of doing is to clamp the aorta above the renals, and use the narrow brim of good tissue for the anastomosis (which now, with the clamp out of the way, can be sewn easily). The 10-20 minutes consumed in making the aortic anastomosis will be well tolerated. But here another danger arises. By placing the sutures in a line immediately adjacent to the renal arterial ostia a line of clotting may be initiated which may grow to occlude the mouth of one or both renal arteries. When this danger seems imminent, it is safer to proceed as if the renal arteries were clearly involved in the aneurysm.

The following case summaries illustrate the problems just discussed.

Case 1 (Figs. 2 and 3).—A 58-year-old man was referred for the treatment of a symptomatic abdominal aortic aneurysm. Physical examination confirmed the presence of a large pulsating abdominal mass that was somewhat tender. Blood pressure and the laboratory findings were normal. Aortography was not done. Laparotomy through a long midline incision confirmed the presence of a large aneurysm extending from the general level of the renal arteries into both common iliac arteries. A moderately extensive dissection led to the conclusion that both renal arteries originated in the wall of the aneurysmal sac, although the relationships of the right renal vessels were not precisely defined. It was thought that resection at this time was not advisable, since the time

Fig. 2 (Case 1).—When only one renal artery is given off from the aneurysmal segment of the aorta and there is room for placing the clamp below the uninvolved renal artery (*a*), bypassing the aneurysm is not necessary. The two anastomoses (aorta to prosthesis and one renal artery to prosthesis) can be performed within the limits of the safe aortic occlusion time, 30 minutes. After these two anastomoses have been completed, the aortic clamp (this time a rubber-shod Kelly clamp) is moved down to the prosthesis below the involved renal artery (*b*), and attention is turned to the distal anastomoses. (S. M. A., Superior mesenteric artery; L. R. A., Left renal artery. In this instance, the right renal artery had an abnormally high origin, coming off directly below the level of superior mesenteric vessel.)

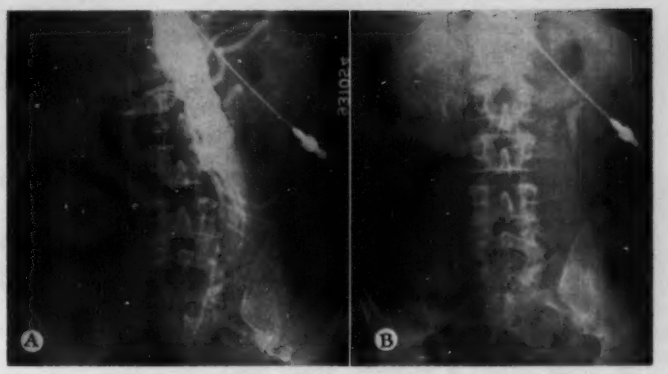

Fig. 3 (Case 1).—The postoperative aortogram (*a*) and excretory pyelogram (*b*) in same case as shown in Figure 2. Open left renal artery and good renal function on the left.

needed for the reimplantation of the renal arteries would exceed the safe limit of allowable aortic occlusion time, and since special preparation had not been made for bypassing the aneurysm. One week later, after prompt recovery from the first operation, the patient was again operated on. Through a thoracoabdominal incision the large visceral arterial trunks of the abdominal aorta were identified. Now it became clear that, owing to an abnormally high origin, the right renal artery was free of the aneurysmal sac, being located about 2 cm. above the upper border of the latter, in close proximity to the superior mesenteric artery. Because of these anatomical circumstances it was possible to apply an aortic clamp distal to the right renal artery, permitting normal inflow into the celiac axis, superior mesenteric artery, and right renal artery. The aorta was cut across, and the prosthesis was sutured to the proximal aortic stump, after which the left renal artery was reimplanted into the prosthesis. The total occlusion time of the left renal artery was 30 minutes. Patient made an uneventful recovery and both aortograms and pyelograms showed a functioning left renal artery 12 weeks postoperatively.

Summary.—In a case of large abdominal aortic aneurysm the high anatomical location of the right renal artery spared it from being encompassed in the aneurysmal sac. It was possible to excise the aneurysm and to reimplant the left renal artery without diverting the aortic blood. The left renal artery was occluded for 30 minutes without ill effects.

Case 2.—A 50-year-old white man was referred for the treatment of an asymptomatic abdominal aortic aneurysm. There had been a history of chronic glomerulonephritis of several years' duration with moderate arterial hypertension. An aortogram disclosed that the aneurysm extended close to the renal arteries but left a short aortic stem free just distal to these structures. After the aortography slight elevation of the serum creatinine was noted (from 0.6 to 1.3 mg. per 100 ml.), which failed to recede in six days. At the time of laparotomy the aneurysm was found to protrude over the posterior aspect of the aorta for a short distance above the renal arteries. In order to complete the freeing of this portion of the aneurysmal sac it became necessary to place a clamp on the aorta above the renal arteries for 32 minutes. In other respects the resection of the lesion was carried out without misadventure and with dispatch. Postoperatively severe oliguria developed which showed only slight improvement in six days, after which it worsened. The uremia that had developed deepened, and the patient died on the 10th postoperative day with the clinical picture of what was believed to have been ischemic renal cortical necrosis.

Summary.—Technical difficulties undisclosed by aortography made it obligatory to cross clamp the aorta above the renal arteries for 32 minutes in a patient with known chronic renal disease (glomerulonephritis) of moderate degree. Ischemic necrosis of the renal cortex ensued that caused death on the 10th postoperative day. The so-called safe limit of aortic occlusion time is evidently shorter for diseased than for relatively normal kidneys.

Case 3.—A 64-year-old man was referred for the treatment of a symptomatic abdominal aortic aneurysm. The blood pressure was 180/100 and the laboratory findings were unremarkable. Aortography showed the presence of a large aneurysm of the abdominal aorta that reached to the immediate vicinity of the right renal artery. A 10-minute excretory pyelogram revealed no excretion of dye in the right kidney. At laparotomy it was found that the aneurysm began directly below the origin of the right renal artery; the left renal artery was well above the aneurysm. By fastidious dissection a very short segment of aorta could be isolated distal to the right renal artery,

but in order to use the narrow (0.5 cm. wide) brim of aortic wall for anastomosis the clamp had to be placed between the two renal arteries, thus occluding the right one for 30 minutes. The sutures passed through a line that was directly adjacent to the ostium of this vessel. The patient did poorly after the operation, became oliguric, and died on the second postoperative day. The cause of death was myocardial infarction, but at autospy the additional finding was made of a recent thrombosis of the right renal artery with renal infarction, the thrombus having arisen from the aortic suture line. The left kidney was unaffected.

Summary.—Placing of the suture line between the aorta and the graft near the mouth of right renal artery resulted in thrombosis of this vessel. Resection of the aorta at a slightly higher level and reimplantation of the renal artery might have been a better choice of procedure.

Infrarenal Clamping of the Abdominal Aorta.—The clamping of the abdominal aorta below the level of the renal arteries may affect the kidneys in a number of ways.

When a clamp is placed across the aorta at the infrarenal level a rise in the systolic blood pressure ensues, which varies in magnitude and duration but which is, as a rule, readily compensated for. The kidneys, of course, participate in receiving whatever harmful effects may result from the persistence of this systemic arterial hypertension. Even in the absence of systemic hypertension, however, the blood pressure within the renal arterial tree may rise, owing to possibly two reasons. With a distal clamp on the aorta the renal arteries now receive the full terminal impact of the kinetic energy of the moving blood. Secondly, it has been postulated that the placing of the clamp distal to but close to the renal arteries elicits a reflex vasospasm in the renal arterial tree.[1,2] (The claim has also been made that this reflex spasm can be abolished with sympatholytic drugs.[1,2]) Moreover, the altered hemodynamics of the blood flow in the renal arteries under these circumstances may also be significant; the increased turbulence may lessen the volume-flow.

Just how important clinically any of these effects is cannot at this time be precisely stated. Many cases in which the aortic clamp had been placed close below the renal arteries for periods of time ranging up to 90 minutes show no postoperative clinical impairment of renal function and, conversely, in most of the cases with postoperative decrease of renal efficiency, factors other than the effects of aortic occlusion can be readily demonstrated. It can safely be concluded, however, that the presence of the clamp on the infrarenal aorta creates an unphysiological state and that all effort should be made to diminish the duration of the clamping and its proximity to the renal arteries.

Some other harmful effects of the clamping of the aorta near the renal artery should be mentioned although these are occasioned not by intrinsic physiologic derangements but rather by technical imperfections. The renal arteries may be inadvertently distorted or kinked by hasty or unskillful application of the clamp, and the aorta itself may be traumatized. Both these errors must be assiduously avoided.

The outcome of the following case may have been due to the effects of infrarenal aortic clamping.

CASE 4.—A 57-year-old man was referred for the treatment of a known symptomatic abdominal aortic aneurysm. Patient had had a left nephrectomy for hypernephroma 12 years previously. There was no known evidence of recurrence. On physical examination there was a pulsating abdominal mass. The blood pressure was 180/100 mm. Hg. Electrocardiogram showed left ventricular hypertrophy. Function of the remaining kidney was found to be within low normal limits by the creatinine excretion test and intravenous pyelography, but there was a significant transitory rise in the serum creatinine following an aortogram. In the aortograms the aneurysm was found to be infrarenal, and a good distal outflow tract was demonstrated. During the aneurysmectomy 10 days later there were no technical complications but there was a persistent increase in the blood pressure during the period of aortic clamping which lasted for 45 minutes. Postoperatively the patient was oliguric and, although the urinary output gradually increased, his condition rapidly deteriorated. Death occurred on the ninth postoperative day in a state of severe uremia. Autopsy revealed acute cortical necrosis of the right kidney. (Residual hypernephroma was found in the region of the left kidney.)

TABLE 1.—*Case Showing Significant Reduction in Creatinine Clearance After Translumbar Aortography*

Woman, age 41, — Aorto-iliac occlusive disease. Three injections of 70% sodium acetrizoate (total amount 80 ml.) I. V. thiopental sodium anesthesia.

Urinalysis										
Before		After		Cr. Cl. Ml/Min.			S. Cr. Mg/%		15′ PSP	
Alb.	Sed.	Alb.	Sed.	Before	After	%-Drop	Before	After	Before	After
0	0	3+	RBC	122	33	75	0.6	2.3	34%	6%

Note: Cr. Cl. returned to normal on 11th postaortogram day. Subsequent uneventful resection of aortic bifurcation.

Summary.—The type of renal damage—cortical necrosis rather than lower nephron degeneration—and the lack of other factors that could have been responsible for the outcome of this case suggest that renal ischemia was the initial insult. The only physiological changes detectable that can have resulted in renal ischemia were those of altered hemodynamics brought about by clamping of the aorta below the renal artery.

The Effects of Contrast Media

While the harmful effects on renal function of the injection into the aorta of contrast media is by no means one of the most important dangers of aortography, its existence is well ascertained and its significance is far from negligible. In a careful study of 50 cases with aortograms by means of 70% sodium acetrizoate (Urokon) among our own patients, 18% showed significant depression of postaortography renal function.[3] No fatality was caused; indeed no permanent damage was noted. It was observed, however, that in many instances the decrease of renal function lingered for 48 or even 96 hours, and in one unusual case the functional depression lasted 11 days (Table 1). It was plain to see that, were such a patient soon after aortography subjected to aortic resection, the risk of postoperative renal complications would be perceptibly increased.

Since it seems quite probable—though not entirely certain—that the impairment of renal function after translumbar aortography is the result of the chemical trauma to the renal epithelium (probably, mostly glomerular epithelium) brought about by the flooding of the organ with an irritant solution, the measures to decrease the harmful effect should aim at the reduction of the toxicity of the contrast agent and at technical steps that would lessen the amount of the agent coming into contact with the renal parenchyma.

Unfortunately, all presently available contrast media are toxic to some degree and they are all irritant to the renal epithelium. There is good evidence,[4] however, that diatrizoate (Hypaque) sodium is probably the least damaging, and this agent is at present the one of choice (Table 2). There is also some experimental evidence to show that a state of good hydration at the time of the injection of a contrast medium somewhat lessens the nephrotoxic effect.[5] There are also efficacious technical details that reduce the amount of contrast dye reaching the kidneys. We have found, for instance, a significantly smaller incidence of rise in blood creatinine in patients whose aortograms were obtained through a so-called "low puncture," that is, by inserting the needle into the aorta midway between the bifurcation and the renal arteries rather than at a suprarenal level (Table 3). We are using this technique now in all cases of

TABLE 2.—*Renal Function Study Following Lumbar Aortography: Suprarenal Injection*

Medium	Amount Injected	No. of Procedures	No. with Increase of Serum Creatinine Greater than 0.5 Mg. %
Acetrizoate 70%	50 to 100 cc.	50	9 (18%)
Diatrizoate 70%	30 cc.	62	4 (6.4%)

TABLE 3.— *Renal Function Study Following Lumbar Aortography: Suprarenal and Infrarenal Injection*

Medium	Technique	No. of Procedures	No. with Increase of Serum Creatinine Greater than 0.5 Mg. %
Diatrizoate 70%	Suprarenal	62	4 (6.4%)
Diatrizoate 50%	Infrarenal	38	1 (2.8%)
Total		100	5 (5.0%)

TABLE 4.—*Anomalies of Renal Anatomy in 250 Cases of Operative Dissection of the Abdominal Aorta*

Type	No.	Examples
Morphological	2	Horseshoe kidney Left renal agenesis
Arterial	6	Persistent segmental renal arteries
Venous	3	Retroaortic left renal vein
Total	11 (4.4%)	

occlusive disease in which at least one femoral artery is palpable. A most important factor for reducing renal damage is the limitation of the amount of the injected dye to the minimum compatible with obtaining films of diagnostic quality. For this end, besides a reasonable degree of skill on the part of the operator, good equipment for sequential multiple exposures is essential. Such equipment does away with inaccuracies in timing the exposure, which is the greatest source of need for repeated injections. Indeed, if for any reason good angiograms cannot be obtained with the predetermined maximum allowable amount of dye (which in the case of 70% diatrizoate sodium is 25 cc.), it is much safer to postpone the repetition of the examination for another day.

Since some renal effects may occur in spite of all these safeguards, it is highly recommended that the state of renal function be followed before and after aortography with the help of some simple but reliable function test. We have found the serum creatinine level most satisfactory for this purpose. The determination of this blood component is a part of the patient routine work-up and is repeated daily until it returns to its preaortogram level. This precaution is of particular usefulness in patients with known renal disease. Obtaining excretory pyelograms 10 minutes after the intra-aortic injection of the contrast medium is also a good precautionary practice.

Problems Arising from Renal Anatomy

Problems of this origin fall into two groups. In one group the technical difficulties stem from the presence of a developmental anomaly; in the other, from the topographic proximity of the ureters to the aortic aneurysm.

Vascular Developmental Anomalies

Arterial Anomalies.—The most frequently seen vascular developmental anomalies in the group under study were arterial. Among the 250 operative aortic dissections 6 such instances were noted (Table 4).* A detailed description of the embryological events that lead to the persistence of supernumerary or aberrant renal arteries[6] is beyond the province of this essay, but it may be recalled that the primitive kidneys (mesonephroi) in early embryonic life are supplied by a series of paired mesonephric arteries arising from the aorta. As the metanephros ascends from the pelvis to occupy its ultimate position in the upper abdomen its vascular connections with the aorta gradually disappear until only the mature renal artery remains. If any of the early renal arterial connec-

* The reliability of such dissections needs to be discussed briefly. Since we always define the renal arteries and the left renal vein when contemplating a surgical procedure on the aorta, it is safe to say that no aberrant arterial branches coming off the aorta between the renal arteries and the bifurcation were overlooked in these cases. There may well have been accessory arterial branches above the level of the renal arteries that were not exposed to view; however, the preoperative aortograms would probably have shown the presence of these. In any case, aberrant arteries of the last-named type have small practical importance.

tions persist, the adult kidney will have one, or more, supernumerary artery. The so-called accessory renal arteries are thus in truth persistent segmental renal arteries. They may occur on either side of the aorta and at any level between the diaphragm and the aortic bifurcation but are commonest in the region of the lower kidney poles.

The practical importance of these anomalous renal arteries in aortic surgery is twofold. In the first instance, being in unpredictable anatomical locations, they may be injured in course of surgical dissection in spite of the exercise of ordinary care. Secondly, accessory renal arteries may complicate surgical procedures in the proximity of the usual anatomical position of the renal arteries. As regards the first-named eventuality, a preoperative aortographic survey usually provides forewarning of the presence of the vascular anomaly. Occasionally, however, even aortography of good quality may fail to visualize aberrant renal vessels of clinical importance. It is advisable, therefore, to keep in mind constantly the normal arterial anatomical pattern as the aorta is dissected free and to identify any vascular branch that does not accurately fit the conventional picture. The inadvertent neglect of this precaution led to a most unusual complication in the following case.[7]

CASE 5.—A 59-year-old man was referred for the treatment of an asymptomatic abdominal aneurysm. Aside from the findings of a pulsating midabdominal mass the physical examination was not remarkable. The blood pressure was 130/80 mm. Hg. The results of the routine laboratory studies were within normal limits. A translumbar aortogram was performed, demonstrating a typical infrarenal aortic aneurysm, and surgical treatment was advised. At the time of operation while the anterior surface of the aneurysm was being dissected at a point approximately 2 cm. distal to the level of the left renal vein, an artery 5 mm. in diameter was inadvertently incised. Repair was easily accomplished with three interrupted 5-0 silk arterial sutures. Further dissection identified this artery to be an aberrant main right renal artery. The aneurysm was resected and replaced with a fresh aortic homograft. At the close of the operation the right renal artery was pulsating normally. Postoperatively the blood pressure steadily rose, reaching a level of 250/176 on the fourth day. At this time acute pulmonary edema developed, which responded to morphine sulfate, oxygen, aminophylline, and digitalization. The postoperative course was further marred by a small anterior myocardial infarction on the ninth postoperative day. In an attempt to reduce the blood pressure a Rauwolfia derivative (Reserpine), hydralazine hydrochloride (Apresoline) and chlorisondamine chloride (Ecolid) were given but were ineffective in bringing about any significant blood pressure reduction. By the 15th postoperative day it was clear that, since medical therapy had been ineffective and since intravenous pyelography had shown the left kidney to be functionless, in spite of the patient's cardiac status nephrectomy would have to be done in an attempt to correct the malignant hypertension. At the time of nephrectomy the right renal artery was found to be thrombosed, but the right renal vein was patent. No accessory renal artery was identified. The removed kidney was, as a whole, pale grayish pink, soft and slightly enlarged. About 30% of the cortical surface showed areas of infarction that were seen to extend into the medullary substance on cut section. Half of the kidney was submitted to Dr. George Wakelin for an assay of its renin content, which was found to be 3.4 dog units per gram, a striking increase over the normal value of 0.1 unit per gram. Following nephrectomy there was an immediate fall of the blood pressure to 120/72. Hypotension ensued, and for the first two days the blood pressure was supported by vasopressor medication. On the third day the blood pressure was 200/90 and then it fell spontaneously to a level of 130/80 at the time of discharge 20 days later. Blood pressure recordings 2, 3, 12, and 30 months after nephrectomy were consistently near 130/80 or lower. At the present time patient is carrying on a full university teaching schedule.

Comment.—Aside from being an example of the hazards of injury of which aberrant renal vessels are susceptible, this case represents the only recorded instance of a so-called "Goldblatt kidney" in man.

With regard to the second difficulty created by the presence of accessory renal arteries (namely, when they arise near the usual anatomical location of the renal arteries), the problem faced by the surgeon is that of deciding the functional importance of the aberrant vessel. In this regard it is well to remember that accessory renal arteries are end-arteries, without intercommunications with the main renal artery, and that in spite of their small size they may be responsible for the blood supply of a

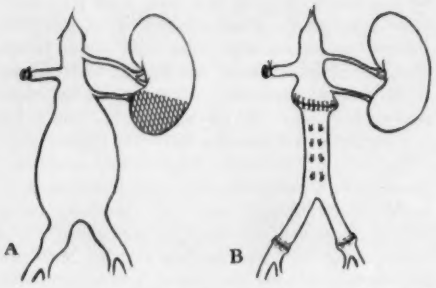

Fig. 4 (Case 6).—An instance in which the presence of an accessory renal artery forced a fatal compromise in surgical technique. Resection of the aneurysm would have posed no problem if it had been possible to transsect the aorta distal to the left renal artery. This was not deemed safe since (1) the opposite kidney had been removed; (2) the accessory renal artery was demonstrated to supply the lower one-third of the remaining kidney, and (3) the accessory renal artery was too small for reanastomosis. The proximalmost part of the aneurysm (which appeared reasonably well preserved) was used for anastomosis; it ruptured on the ninth postoperative day, with swift fatal hemorrhage. (*a*) Preoperative. (*b*) Postoperative.

relatively large portion of the kidney parenchyma. When the latter is the case, the sacrifice of the branch may be disastrous, particularly if the other kidney is absent or if there is significant impairment of the renal function. Yet in some cases of aneurysms, where the infrarenal aortic segment suitable for anastomosis is short, without the tying of the accessory branch a satisfactory anastomotic procedure cannot be performed. The following case (Fig. 4) illustrates this problem.

Case 6.—A 63-year-old man was referred for the treatment of a known abdominal aortic aneurysm that had been wrapped with cellophane five years previously. On physical examination a large nontender pulsating abdominal mass was easily felt. Blood pressure was 140/90 mm. Hg. The electrocardiogram was not definitely abnormal. A translumbar aortogram showed the aneurysm to extend proximally to the immediate vicinity of the renal arteries. Since suprarenal clamping of the aorta appeared inevitable for the resection of the aneurysm, it was planned to reduce the occlusion time by first doing a left splenorenal arterial shunt. At the time of abdominal exploration, however, a neoplasm was discovered replacing most of the right kidney. The neoplasm was judged to be a malignant nephroma, and the right kidney was removed. Further surgical intervention at this time was judged to be inadvisable in view of the unfavorable outlook of the kidney neoplasm and, particularly, owing to the reduced renal function resulting from the right nephrectomy. After an interval of six weeks, during which the remaining left kidney was observed to assume excellent compensatory function, the abdomen was again opened and resection of the aneurysm was undertaken. The dissection for the identification of the left renal artery disclosed that the left kidney was supplied by two arterial branches, a proximal one corresponding to the usual anatomical location, originating directly at the upper border of the aneurysm, and a distal one given off from a point 2 cm. below and lying within the outline of the aneurysmal sac. Temporary clamping showed that the accessory arterial branch, although only 2 mm. in diameter, was the only vascular supply to the lower one-third of the kidney. Because of the reduced renal functional reserve already existing it was thought unjustifiably risky to sacrifice this branch, and the choice was made of using the proximalmost portion of the aneurysmal sac for the anastomosis, leaving in this manner the aberrant artery intact. The replacement of the aneurysm with a homograft was carried out without incident, and the patient's recovery during the first eight postoperative days was prompt and uncomplicated. On the ninth postoperative day patient died, before any curative measures could be taken, from a rapid and massive hemorrhage from a rupture of the diseased aorta just above the suture line (demonstrated at autopsy).

It would, of course, seem the lesser of two evils in such a situation to sacrifice the accessory artery if this makes a secure anastomosis possible and if there is reasonable assurance that the minimal needed degree of renal function is not compromised.

The topographic relationships of a case in which the presence of accessory renal arteries seriously restricted the choice of operative procedure are shown in the aortogram in Figure 5.

Venous Anomalies.—The potentially hazardous venous anomalies of the kidneys are the retroaortic location and retroaortic communications of the left renal vein. The presence of the retroaortic location of the renal vein, which occurred three times in this group of cases, is explained by the development of the inferior vena cava from the primitive cardinal veins.[8,9] (Kindred developmental aberrations are the formation

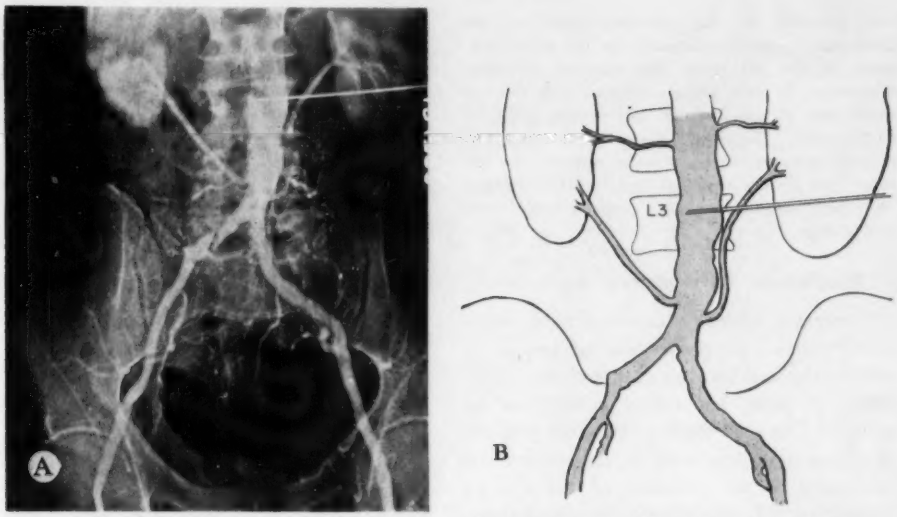

Fig. 5.—Bilateral aberrant renal arteries originating near the bifurcation and associated with right iliac occlusive disease. Without a serious risk, the procedure of choice for the treatment of the occlusive lesion (an aortofemoral bypass) could not be performed since it required clamping of the aorta above the aberrant renal vessels. The only safe procedure commensurate with the degree of existing disease was an endarteriectomy which was ill suited for the case and was unsuccessful. (*a*) Aortogram. (*b*) Artist's drawing of aortogram.

of a circumaortic venous ring and communications between the vertebral venous system and the left renal vein, which, however, were not observed in this series.) The danger for the surgeon lies in the possibility that, in dissecting the dorsal aspect of the aorta, the retroaortic renal vein may be injured, or taken for a vertebral vein and clamped, errors that will usually result in the loss of the kidney. The safest way of avoiding such a mishap is to identify the renal vein in any dissection of the aorta carried above the origin of the inferior mesenteric artery. If the renal vein is not found in its normal anatomical position, it must be searched for in a retroaortic location.

Case 7 (Fig. 6).—A 64-year-old man entered the hospital with a three-week history of lower abdominal pain which radiated to the back and right testicle. Physical examination revealed the presence of a pulsating abdominal mass typical of an aortic aneurysm. The blood pressure was 140/95 mm. Hg. Electrocardiograms showed evidence of an old anterior myocardial infarction with left ventricular hypertrophy. The results of the routine laboratory work were within normal limits. An aortogram was not performed as the history and physical findings were typical of an expanding abdominal aortic aneurysm, and surgical treatment was advised. At operation an aortic aneurysm was observed extending from 2 cm. below the renal arteries and involving the right common iliac artery. After dissecting free the duodenum, which

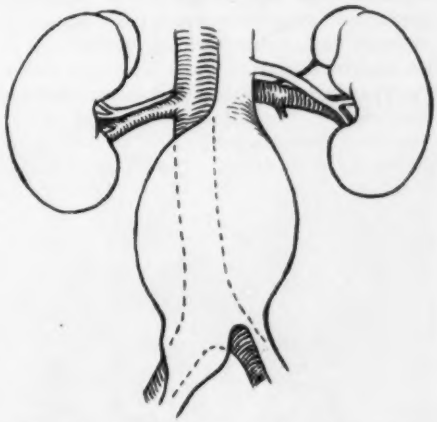

Fig. 6.—Retroaortic left renal vein, a not uncommon vascular anomaly. In all surgical procedures requiring dissection of the aorta above the inferior mesenteric artery it is well advised to identify the left renal vein as a routine matter. If it is not present in its usual position, a retroaortic position must be thought of.

was adherent to the anterior aspect of the aneurysm, a search was made for the usual landmark of the left renal vein crossing the aorta anteriorly. It soon became obvious that the left renal vein in this instance was passing posterior to the aorta. The dorsal aspect of the aorta was defined with caution from below upward, the left renal vein clearly identified, and the resection and replacement of the aneurysm completed. Recovery was prompt.

Morphologic Developmental Anomalies

Horseshoe Kidney Associated with Aortic Aneurysm.—This association of lesions is noteworthy not because of the clinical difficulties it poses but rather because of its rarity.[10] The only serious technical problem one faces in dealing with such a combination of lesions is the selection of the site of transection of the isthmus of the kidney. The correctness of this selection is of great importance, since escape of urine from the cut and sutured end of either kidney might well be disastrous in a vascular operation.

Case 8 (Fig. 7).—A 58-year-old man was referred for treatment of an abdominal aortic aneurysm. The physical examination confirmed the presence of a pulsating abdominal mass. Hypertension of 210/120 mm. Hg. was noted. The electrocardiogram showed evidence of an old posterior myocardial infarction. The results of the laboratory tests were within normal limits. A translumbar aortogram revealed a fusiform aortic aneurysm with rather extensive involvement of the common iliac arteries. An unexpected finding was the presence of a horseshoe kidney overlying the aneurysm. The first step at operation was to free the infrarenal aorta proximal to the isthmus of the horseshoe kidney. The kidney was then divided in the midline, and after the cut ends were wedged, a tight capsular closure was carried out on each cut surface. After division of the horseshoe kidney the two kidneys could be easily retracted laterally, and the resection of the aneurysm was completed in the usual manner. The replacement functioned well; wound healing was normal, and no renal complications developed.

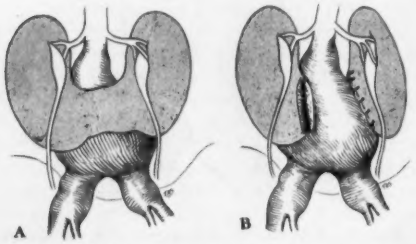

Fig. 7.—Aneurysm of abdominal aorta with horseshoe kidney. (*a*) In the management of an aorta aneurysm associated with a horseshoe kidney, the isthmus of the kidney is bisected, the cut ends sutured, (*b*) and the removal of the aneurysm is then completed.

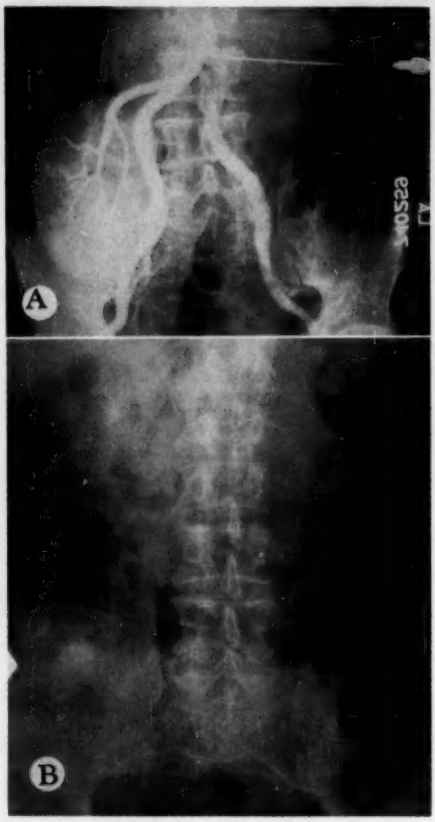

Fig. 8.—Pelvic kidney with agenesis of the contralateral kidney. (*a*) Aortogram. (*b*) Pyelogram.

Ectopia and Crossed Ectopia of the Kidneys.—Unusual technical problems have been posed in two cases, not yet operated on, with vascular lesions associated with a pelvic kidney and a crossed renal ectopia,[11] respectively, as shown in Figures 8 and 9.

Ureteral Obstruction

The ureters, particularly the left one, are close enough to the aorta to be encroached upon by many large aneurysms. Since, how-

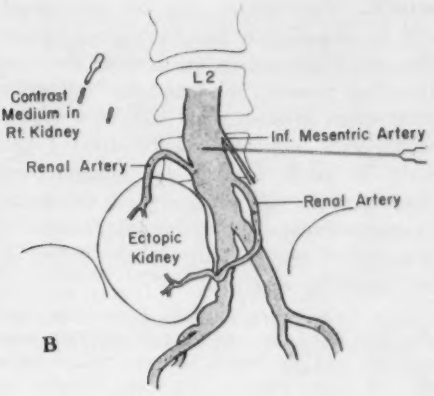

Fig. 9.—Crossed renal ectopia. Both kidneys are on the right, one being pelvic in location. (*a*) Aortogram. (*b*) Artist's drawing of aortogram.

ever, they are cushioned posteriorly by a thick pad of soft tissues, the presence of even a large aneurysm causes obstruction only in special circumstances. One such circumstance is the extension of the aneurysm distalward into the direction of the common iliac arteries, when the aneurysmal mass may press the ureters against the lateral border of the lumbar spine as they begin to curve inward to cross the common iliac

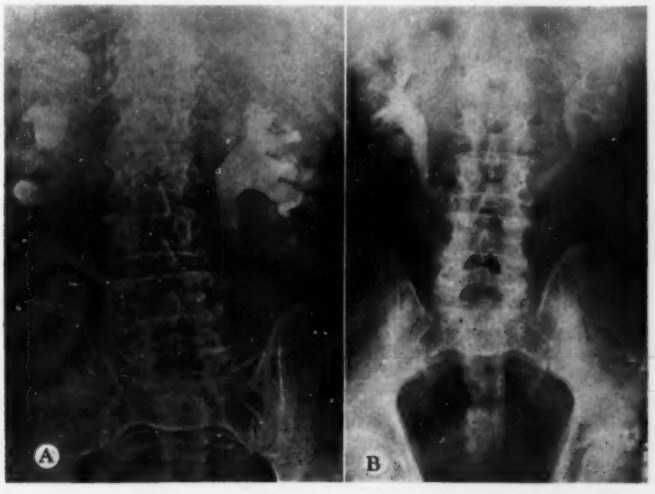

Fig. 10 (Case 9).—Excretory pyelograms. (*a*) Preoperative. (*b*) Postoperative.

arteries. The ureters may be compressed also by an aneurysm that has elicited a great deal of inflammatory exudate in the surrounding tissues. This condition will arise most often in aneurysms that have slowly ruptured or that have had dissection. Especially in the latter type, the inflammatory fibrosis about the periphery of the aneurysmal sac may assume the appearances of a woody phlegmon. This was the finding in the following case (Fig. 10).

CASE 9.—A 60-year-old man entered the hospital with left costovertebral angle and flank pain radiating into the lower abdomen, left testicle, and left medial aspect of the thigh. On physical examination diffuse abdominal tenderness with left costovertebral-angle tenderness were found. No abdominal mass was felt. The blood pressure was 140/90 mm. Hg. The laboratory findings were not abnormal. Excretory pyelograms showed mild evidence of hydronephrosis bilaterally with a greater change in the left kidney. Patient's fever, which had been as high as 101 F., gradually became normal. The abdominal and left flank pain continued. No definite diagnosis was established, and patient was discharged. Two weeks later he was readmitted because of an exacerbation of his pain in the right costovertebral angle, low back, and abdomen. Physical findings revealed generalized abdominal guarding, no mass, a temperature of 99.6 F., and a blood pressure of 170/100 mm. Hg. An extensive diagnostic investigation was carried out; complete gastrointestinal radiography, lumbar puncture, and blood chemical studies were entirely negative. Excretory and retrograde pyelograms, however, demonstrated the presence of bilateral hydronephrosis with narrowing of both ureters at about the level of the fourth lumbar vertebra. The impression was gained that the patient had a retroperitoneal neoplasm with associated ureteral obstruction, and laparotomy was advised. At operation an abdominal aortic aneurysm of moderate size was found. The vascular swelling was completely buried in an expanse of inflammatory changes. The retroperitoneal adipose tissue was matted into a hard mass. All anatomical landmarks around the aortic swelling were obliterated. The operator deemed the technical problems of resection prohibitive and decided to delay the definitive surgical treatment. Patient made a swift recovery from the operation. With his symptoms much improved and his NPN down to 46 mg. % from the previous 63 mg. %, he was discharged. After one month there had been enough improvement in his general condition to permit preparations for the resection of the aneursym. A translumbar aortogram disclosed the aneurysm to be infrarenal. In-lying ureteral catheters were placed for drainage and as operative guides. The NPN at this time was 27 mg. %. At operation it was observed that there had been considerable healing of the retroperitoneal phlegmon and that the size of the aneurysm had decreased. The ureters were dissected free from their adherence to the aneurysm wall, the aneurysm was resected and a bifurcation homograft was inserted. Recovery was uncomplicated. The pathologic examination of the aneurysm showed that the swelling had been caused by the dissection of the layers of the aortic wall by the blood stream that had entered the subintimal space through an atheromatous ulceration 10 cm. proximal to the aortic bifurcation. Intravenous pyelograms six weeks later showed marked improvement in the hydronephrosis. A translumbar aortogram six months postoperatively demonstrated a well-functioning aortic bifurcation homograft; excretory pyelograms at this time were considered normal except for slight hydronephrosis on the right side. Patient returned to his work as wall painter. Two years postoperatively aortographic appearances were satisfactory. Aside from a small myocardial infarction, from which recovery was prompt, the patient has continued to do well up to three years postoperatively.

This case illustrates the preferred method of approach to such a complication. In the treatment of an abdominal aortic aneurysm with unilateral ureteral obstruction we applied a different principle. Since the patient represented a markedly impaired risk and since the obstructed kidney showed evidence of infection with practically no pyelographic function, a nephrectomy was first performed. The pathological examination of the kidney strongly suggested that the changes had been reversible. Aneurysmectomy with the attendant relief of the obstruction of the ureter probably could have saved the kidney.

Summary

Certain problems related to renal physiology and anatomy that arise in surgery of the abdominal aorta are discussed. Some aspects of renal ischemia caused by cross clamping of the aorta and of the effects of angiographic contrast media on renal function are described. Instances of technical difficulties due to vascular anomalies (aberrant renal arteries and vein) are cited. Ex-

amples of the association of abdominal aortic aneurysm with horseshoe kidney and with ureteral obstruction are given. The following conclusions are offered:

Although cross clamping of the aorta distal to the renal arteries has not been found responsible for any specific physiologic injury, its harmful potentialities must be kept in mind.

The safe period of cross clamping of the aorta above the renal arteries has been found to be about 30 minutes for kidneys without manifest organic disease. In operative procedures requiring longer clamping, renal circulation must be maintained by some form of bypass.

In aortography, the use of the least toxic contrast medium, in the smallest possible amount, with multiple exposure technique for the avoidance of repetition of injection is recommended. The usefulness of the pre- and postaortographic serum creatinine as functional index of renal function is stressed.

In course of operative dissection of the abdominal aorta the possibility of the presence of accessory renal arteries must be remembered. Whenever the aortic dissection reaches above the level of the inferior mesenteric artery, the left renal vein must be looked for, and if it is not found in its normal anatomical location must be sought in a retroaortic position.

In dealing with horseshoe kidneys associated with an aneurysm of the abdominal aorta, bisection of the renal isthmus, suture of the cut ends, and resection of the separated kidneys allow the removal of the aneurysm in the routine manner. When an abdominal aortic aneurysm is complicated by ureteral obstruction, the resection of the aneurysm at the earliest safe moment is indicated.

Henry Ford Hospital.

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DISCUSSION

ON PAPERS BY DRS. CAMMACK, RAPPORT, PAUL, and BAIRD, AND BY DRS. SZILAGYI, SMITH, AND WHITCOMB

DR. L. CHANDLER ROETTIG, Columbus, Ohio: I would like to compliment Dr. Cammack, Dr. Rapport, Dr. Paul, and Dr. Baird on their paper. Certainly, with 400 deaths due to automobile accidents occurring on an average holiday week end, this type of laboratory and clinical investigation is sorely needed. It is this type of approach and research which will help us to deal with the many cases of severe chest trauma which we see and which may enable us to save more of these lives.

The members of the Thoracic Surgery Section of Ohio State University in Columbus have been intensely interested in the problems of chest trauma for a number of years. I would like to recall that at the meeting of the American Association for the Surgery of Trauma three years ago, we advocated

the early operative management of penetrating wounds of the chest and suggested that it would greatly reduce the morbidity in these injuries and probably save some lives. At last year's meeting of the Central Surgical Association we reported our investigation and management of the early operation for closed injuries of the chest for bronchial rupture. I think that this present paper reinforces the idea that all chest injuries should have a careful but rapid evaluation. A more aggressive attitude should then be applied to the indications for thoracic exploration. Such findings as multiple depressed rib fractures, hemothorax, widening of the mediastinum, cardiac tamponade, and sucking wounds of the chest should be considered as indications of more early and frequent thoracotomy than at the present time.

Since Dr. Karl Klassen, my associate, was unable to attend this meeting I would like to report on his behalf a case which he operated upon about a month and a half ago. This was a 30-year-old white man, who had been injured in an automobile accident approximately eight hours prior to his admission to the hospital. He was transferred to University Hospital from a nearby city. At the time of admission an x-ray of his chest showed a marked widening of the superior mediastinum suggestive of massive mediastinal bleeding. The patient was operated upon shortly after admission and a half-inch tear of the aorta just below the ligamentum was found. Dr. Klassen sutured the tear, and the patient then made an uneventful recovery.

Dr. Josephus C. Luke, Montreal: As part of the discussion of Dr. Szilagyi's paper, I would like to present a method of determination of the degree of renal damage in cases of aortography. By this method one can determine fairly accurately which cases will go on to renal shutdown and consequently be able to initiate immediately treatment in an attempt to minimize this serious complication.

The aortogram should be reviewed immediately after being developed, and, if one sees the kidneys heavily flooded with contract material, then a further plain film should be taken. If in this second film the kidneys still show heavy opacification, then one can be sure that serious damage has occurred. We have followed two such cases by x-ray. In one, the right kidney cleared promptly but the left remained opacified for two days diminishing gradually. The patient's NPN rose; bloody urine appeared, and it was 10 days before the renal disturbance subsided, presumably owing to the functioning right kidney.

In the second case both kidneys and the gallbladder remained well visualized for three days, and, despite immediate papaverine and heparin therapy plus the regular program for renal shutdown, he went on to die of uremia in nine days.

Dr. William H. Meade, Lansing, Mich.: The paper by Dr. Rapport and his conferees interests me because in the past year we have seen three ruptured aortas, and we have recognized the disease at the autopsy table. All of these patients had x-rays of the chest on admission. Two of them had severe multiple injuries, but one man 66 years of age certainly would have had an opportunity to be saved had we recognized his disease.

I was interested in the mechanism of rupture and have read papers on deceleration. However, two of these patients had longitudinal slits behind the common carotid and subclavian. The man 66 years of age had a slit which was 3 cm. in length, and I think he could have been saved.

I would like to call your attention to the fact that a single roentgenogram of the chest immediately after injury is not enough, and that these patients should have roentgenograms daily, particularly if it is noted that they are having some difficulty with respiration.

Dr. Robert P. Hohf, Evanston, Ill.: My remarks are pertinent to the paper by Drs. Szilagyi, Smith, and Whitcomb.

We have been impressed by the two commonest complications following aortic clamping, namely, cardiac and renal difficulties, and, at surgery, have had more trouble when the clamp is released than during the occlusion.

The heart apparently tolerates the clamping period much better than it does the release. The hypotension may be prolonged despite the usual methods of preventing this—lowering the head of the table, giving intravenous infusion of blood, and very slowly releasing the clamp.

In the laboratory we were able to correct much of this difficulty by giving a vasopressor immediately before release of the clamp, thereby limiting the subsequent hypotension and shortening its duration. This, also, has been of use clinically.

Dr. Charles L. Eckert, Albany, N. Y.: I would like to comment on the paper given by Dr. Smith, and on what the last discusser said about the use of vasopressors.

I would like to call attention to the studies carried out in our laboratories by Dr. Sam Powers which relate to the duration of cross clamping of the aorta. In dogs if a clamp is applied to the aorta with or without complete occlusion, over a period of hours there is a striking decrease in renal blood flow. At the same time the mean arterial pressure remains constant, which means that the renal vascular resistance is increased. In these animals progressive renal tubular necrosis subsequently was observed.

These effects could be abolished by the denervation of the kidney or by the use of trimethaphan (Arfonad) camphorsulfonate for sympathetic blockage. Subsequent to these studies we have used trimethaphan whenever the aorta is to be cross clamped, and we have had no further difficulties with acute renal failure, which we felt was attributable to the use of the cross-clamping technique alone, for this will not protect against hemorrhage or other mechanical aspects which may be conducive to renal failure, which Dr. Szilagyi and his group have emphasized in their paper.

DR. ROBERT E. BERRY, Ann Arbor, Mich.: I would like to congratulate Drs. Smith, Whitcomb, and Szilagyi on the excellence of their paper. Their experience in this field certainly makes anything they say worth while listening to.

I arise to make two points. The first has to do with the effect on the elderly arteriosclerotic heart when the aortic clamp is first applied. As long as the clamp is first applied below the renal arteries there would appear to be little problem. But the elderly patient with, for example, a ruptured aneurysm necessitating placing the clamp above the renal arteries, may well be something else. We have experienced one disastrous experience of high clamping followed by a relentless increase in blood pressure and then a sudden death from left ventricular dilation and failure. When faced with a situation perhaps it would be better to simultaneously clamp the inferior vena cava and gradually release it over a period of minutes so as to permit better adjustment of myocardial tissues that have been weakened by attendant arteriosclerotic involvement.

The second point has to do with the oliguria that often attends aortic operations. Since we have been using epidural anaesthesia for aortic resection, severe oliguria has not been the problem that it was previously. Yet certain patients continue to demonstrate a profound postoperative oliguria. The nature of this oliguria is most important, and its significance should be evaluated as rapidly as possible in order to make the differential diagnosis between oliguria on a renal basis (organic damage to the kidney, severe changes in renal hemodynamics) and oliguria due to increased third-space effect and inadequate fluid intake. As the fluid needs of these two totally different oligurias are diametrically opposed, caution is necessary in the administration of parenteral water and salt when a low urinary output is due to renal involvement in order to prevent superimposition of pulmonary or cerebral edema in a patient that has been subjected to an operation of major magnitude.

DR. RICHARD L. RAPPORT, Flint, Mich.: I should like to thank Drs. Roettig and Meade for their comments. We have been aware of Dr. Klassen's success in the management of an acute traumatic rupture of the aorta, and are deeply impressed and indeed delighted with his result. We hope this will encourage more of you to open chests early, as Dr. Roettig mentioned.

We are convinced that early operation in severe closed and open chest injuries will salvage many patients. We realize this is somewhat sacrilegious, but nevertheless we are impressed with the little damage we do to chests that we happen to open unnecessarily, and the regret that we sometimes feel with those we leave for so-called conservative management.

Dr. Meade mentioned longitudinal tears in the retrocarotid area. These are surprising. They are not reported in the literature. Since we left Dr. Paul, who is our engineer, in Flint, I have no further comments concerning the mechanism.

We had hoped to be able to reproduce deceleration injury to the aorta experimentally and to present graphic evidence of the mechanism involved, but to date we have not succeeded in these efforts. Our efforts will continue, and perhaps by next year we may have more fundamental information to give you.

We sincerely hope that if you got nothing more from this paper, you will remember that a steel bar is more elastic than a rubber band.

DR. D. EMERICK SZILAGYI, Detroit: We are sincerely grateful to the discussants because they have brought out some points that we did not have time to touch on.

As you may have noticed, we gave merely samplings of a very large subject. We thought we would cover many points, but each rather briefly, to give a comprehensive view of the problems we were concerned with.

Dr. Luke's suggestion of taking delayed nephrograms is an excellent one, and I may add that the delayed radiogram of the kidneys, besides ascertaining whether the contrast medium has been cleared, also furnishes a good index of the functional state of the kidney through the degree of visualization of the renal pelves.

The question of hypertension on applying and of hypotension on removing the occlusive aortic clamp is a vexing one but one which can be readily managed if one keeps in close touch with the anesthesiologist. The surgeon's maneuvers must be determined by the changes in the blood pressure as recorded almost continuously by the anesthesiologist. Changes will occur in either direction, and unless hemodynamic adjustment takes place very promptly—within two to three minutes—efforts are made to reestablish the normal relationships either by partially reapplying the clamp or by narrowing the graft by finger pressure or administering a vasopressor or a ganglionic block-

ing agent, as the case may be. Most of our concern has been with the fall of blood pressure upon reestablishing circulation through the newly inserted graft. The rise of blood pressure on applying the aortic clamp has been of relatively slight importance, and we have never had the misfortune of seeing acute myocardial failure arise from this transient hypertension, as mentioned by Dr. Berry.

Dr. Powers' work is most interesting. In some instances of long-continued infrarenal clamping of the aorta, the blocking of the sympathetic nerves at the level of the renal pedicle may well be useful.

Dr. Berry also touched upon the problem of anuria following abdominal aneurysmectomy. This is a subject of great complexity and could not very well be included in a discussion primarily clinical in character. I should like to remark briefly that in our experience fatal anuria or oliguria seen after resection of an abdominal aortic aneurysm is usually not primarily a nephrogenic phenomenon but rather a manifestation of a whole array of physiological derangements that supervene after an operative trauma of large proportions, in a patient of advanced years and representing an extremely poor operative risk. A very obvious difference between this type of renal insufficiency and the anuria that may be a primary cause of death is that, whereas patients manifesting the former die within three days after the operation, the latter, if properly managed, seldom leads to death in less than 7 to 10 days.

Revascularization of the Kidney in Hypertension Due to Renal Artery Stenosis

JOSEPHUS C. LUKE, M.D., F.R.C.S. (Eng. and C.), and B. A. LEVITAN, M.D., F.R.C.P. (C.), Montreal

Impaired blood supply to one kidney as a cause of generalized arterial hypertension has been known for many years.[1,2] The classical experiments by Goldblatt[3] in 1934 placed this etiology on a firm foundation. Since then many nephrectomies have been performed for this reason but with cure of the hypertension in only a disappointing minority because cases of renal parenchymal disease as well as those with renal arterial disease were being so treated. Thompson and Smithwick[4] in 1952 found that their best results came when the origin of the renal ischemia was in the renal artery rather than in the kidney proper.

Although nephrectomy is an accepted method of therapy, the vasculature of the kidney removed in cases of renal artery stenosis or occlusion is relatively normal on pathological examination because it has been "protected" from the nephrosclerotic changes incident to the hypertension. The remaining kidney is unprotected. How much better, therefore, to attempt revascularization of the ischemic kidney so as to relieve the hypertension and preserve this normal kidney! Our surgical efforts have been directed in this path, and this presentation concerns our experiences with four patients where renal revascularization has been accomplished.

Selection of Cases

The causes of arterial hypertension are legion and poorly understood, and it should be emphasized that hypertension as the result of renal ischemia due to renal artery stenosis is only a small proportion of the group. Although small, it is a highly important fraction as it is one where dramatic and lasting reduction of blood pressure can be accomplished by proper therapy. The removal of a pheochromocytoma or correction of aortic coarction or Cushing's syndrome are also comparable in this respect. We feel that this group is probably much larger than is reported, chiefly because its significance is not too widely realized and also because, until recently, the investigations necessary to prove the diagnosis were cumbersome and at times indefinite.

Certain points in the history are suggestive of renal artery stenosis, particularly where hypertension begins in children and young adults or relatively suddenly following an attack of acute flank pain. These possibilities, as gleaned from the history, may be listed as follows:

1. Hypertension under the age of 35
2. Moderate hypertension which suddenly gets worse
3. Hypertension unresponsive to hypotensive drugs
4. Hypertension following an attack of flank pain
5. Hypertension associated with Leriche syndrome
6. Hypertension of recent origin

The physical examination is not too helpful with the exception that in renal artery stenosis the diastolic pressure is almost invariably above 110 mm. Hg. The fundi show the usual signs of hypertensive retinopathy, depending on the degree and duration of the hypertension. The urine may be normal or show some albumin and/or red cells and casts. Polyuria due to low specific

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gravity has been reported in cases of acute onset.

Further investigations usually show normal values for blood N. P. N. and a relatively normal pyelogram. Some investigators have stressed that variations in size and shape of one kidney in comparison with the other is of significance, but we have found this to be of little value except where the obstruction of the renal artery is virtually complete. Three special tests are the main diagnostic ones indicating renal artery stenosis. In 1954 Howard [5] demonstrated reduced water and sodium excretion from the ischemic kidney, confirming what others had previously shown in the Goldblatt type dog. This is determined by differential collection studies with catheters placed in each ureter. High-sodium diet is given the patients for several days prior to the test. Creatinine clearance studies can also be made in the same manner as a confirmatory test. Again, differential phenolsulfonphthalein (P. S. P.) excretion can be determined in this manner. All these tests may show decreased values on the affected side, but reduction in both water and sodium excretion is the minimal requirement for diagnosis and is vitiated by any appréciable bleeding or leakage about the catheters.

Brust and Ferris [6] have described a method of detecting the case of hypertension due to renal artery stenosis. When 400 mg. of the ganglionic blockading drug tetraethylammonium chloride (Etamon) is injected by rapid infusion in patients with hypertension of essential or renal parenchymal origin, a marked depressor effect occurs on the blood pressure. In those with renal artery ischemia the B. P. remains level or shows an actual gradual pressor response. Pheochromocytoma may yield a pressor response, but here the rise in the B. P. is abrupt and marked. In the acute phase of nephritis, a pressor response is also obtained, but here the urinalysis is usually diagnostic.

The best indicative test is aortography. The stenotic area may be visualized or, if not, can be assumed because of the presence of a well-marked poststenotic dilatation. The renal size, shape, cortical thickness, and

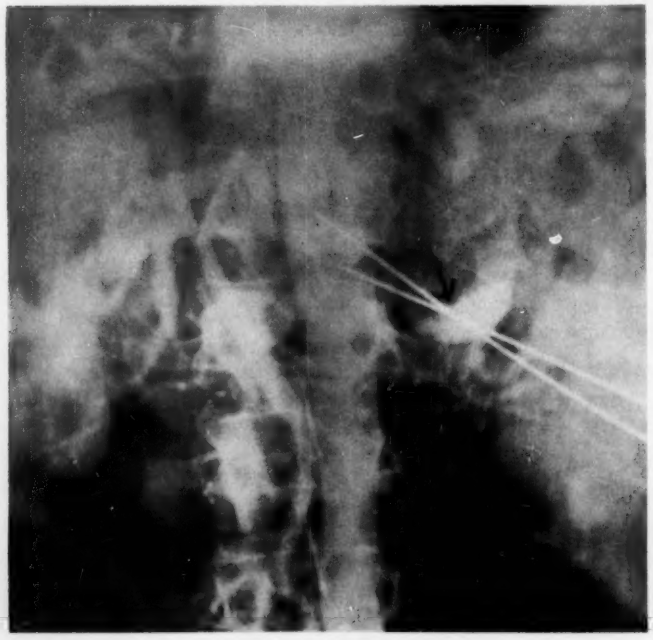

Fig. 1 (Case 1).—Translumbar aortogram demonstrating a large poststenotic dilatation in the left renal artery.

comparative development of the nephrogram can be observed. Arteriosclerotic disease in the aorta and other major branches may be demonstrated. Unfortunately, renal arteriography is not simple and is open to interpretational and technical difficulties. Until recently we employed the translumbar needle technique. Some cases with large poststenotic dilatations were simple in interpretation but others with no such dilatation or with slighter degrees of renal artery notching were difficult to evaluate. At times, try as often as one could, the renal artery filling was insufficient for interpretation. We feel that many of these dubious results are due to the needle bevel in the aorta being pointed in one direction only, and consequently poor mixture of the contrast material with the blood above the renals. At the present time we have changed to the Seldinger[7] technique, where percutaneously a catheter is introduced into the common femoral artery and directed into the aorta to the level of T 11 or 12. The catheter has an end opening as well as multiple side holes to ensure proper diffusion of the contrast material. The automatic injector is used, and exposures are taken each half second on the Elema machine. In this way a much superior renal and splenic artery arteriogram can be obtained.

Report of Cases

CASE 1.—A man aged 51 was admitted to the Royal Victoria Hospital complaining of dizziness, headache, and blurred vision. He was a known hypertensive for 12 years and had had two previous admissions for investigation of this condition. His B. P. in hospital ranged from 170/100 to 220/130 and he had a poor response to antihypertensive drugs. His urine was normal, although he had had two attacks of painless hematuria in the weeks preceding admission. His N. P. N. was 24; the 17-ketosteroids were normal, but the corticoids were elevated. The intravenous pyelogram (I. V. P.) was normal, and differential excretion studies showed decreased P. S. P. excretion from the left kidney. On the other hand, the creatinine clearance was better on the left than the right. The tetraethylammonium test showed a rise in blood pressure over 10 minutes. An aortogram (Fig. 1) showed a poststenotic dilatation in the left renal artery.

The spleen and kidney were approached by a thoracoabdominal incision on June 3, and a hard arteriosclerotic plaque was found in the left renal

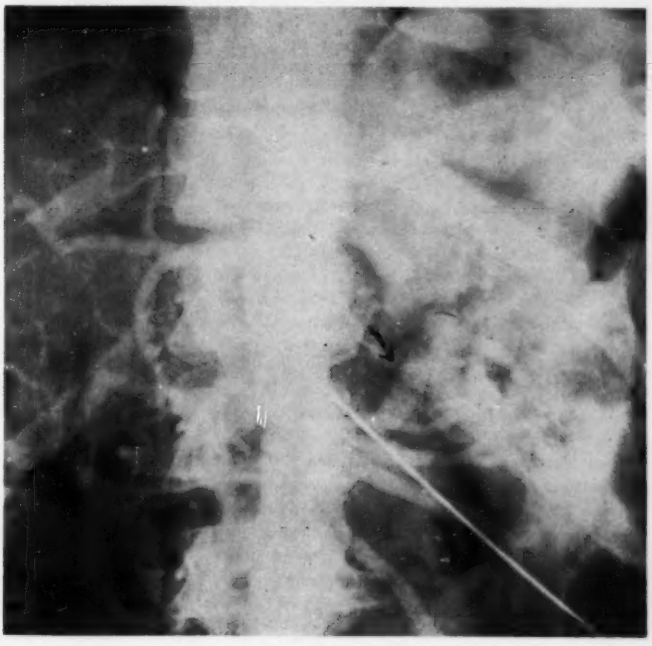

Fig. 2 (Case 2).—Translumbar aortogram demonstrating a moderate-sized poststenotic dilatation in the left renal artery. As in Figure 1, the actual stenosis is not seen.

artery, ¾ in. from the aorta. A well-marked poststenotic dilatation was present with a thrill. The spleen was removed, and the splenic artery dissected free. Arteriosclerotic plaques were also found in this artery, which had to be cut back until a proper-sized lumen was obtained. The involved section of the renal artery was removed, and an end-to-end splenic to distal renal anastomosis done. The renal blood flow was interrupted for 17 minutes.

Postoperatively he had an immediate improvement in vision and also of his former symptoms. His B. P. varied from 160/100 to 120/80. After discharge his B. P. rose to 180/110, but he now responds well to small doses of antihypertensive drugs and is symptom-free.

Case 2.—A man aged 55 was admitted to the Royal Victoria Hospital on July 8, 1958, complaining of symptoms suggestive of disc disease with sciatic pain. His B. P. was found to be 230/160. His urine showed a moderate number of hyaline casts, and blood N. P. N. was 26. He had hypertensive retinopathy Grade 3 on the right and Grade 2 on the left. The Howard test showed marked decrease in water and Na excretion from the left kidney. The creatinine clearance and P. S. P. excretion were also decreased on the left. The tetraethylammonium test showed an initial drop but rose well above the preinjection level in the latter part of the test. Lumbar aortogram (Fig. 2) revealed a well-marked poststenotic dilatation in the left renal artery. Operation was performed on July 10, 1958, again through a thoracoabdominal incision with splenectomy, resection of the involved renal artery, and end-to-end splenic to renal arterial anastomosis. Postoperatively his B. P. varied from 118/70 to 140/100.

He was readmitted for assessment on Oct. 1, 1958, with a B. P. of 145/85. The N. P. N. was 21; I. V. P. normal, and differential excretion studies now all normal for Na, water, and P. S. P. A marked improvement in his fundi was noted.

Case 3.—A man aged 47 was admitted to the Royal Victoria Hospital on Oct. 7, 1958. He was discovered to have hypertension 13 years previously, but had no related symptoms. His urine showed a trace of albumin and occasional hyaline and granular casts. His B. P. varied in hospital from 140/90 to 200/110. Excretion studies showed decreased P. S. P. from the left kidney and also showed decreased water and Na excretion in comparison with the right. The tetraethylammonium test produced a drop in systolic pressure but a slight rise in the diastolic. On the basis of this test he did not fit into the renal artery stenosis group. Aortography was performed on three occasions and each time showed decreased filling of the left renal artery in comparison with the

Fig. 3 (Case 4).—Translumbar aortogram revealing a large poststenotic dilatation of the left renal artery.

right. The left nephrogram was less dense and more delayed than the right. No definite stenosis of the left renal could be seen but the aortorenal junction was not clearly seen. No poststenotic dilatation was seen. On the basis of the differential excretion studies plus the suggestive arteriogram, operation was performed on Oct. 23 through a thoracoabdominal incision. The splenic and renal arteries were smaller than normal and went into intense spasm when handled. Despite a thrill in the renal artery no areas of stenosis could be demonstrated to the aortic junction. The splenic artery was detached from the spleen leaving the latter in situ and was anastomosed end-to-side to the distal renal artery just proximal to its bifurcation.

Postoperatively his B. P. varied from 110/70 to 190/100, and since discharge it has remained slightly lower than in his preoperative state.

Case 4.—A man aged 36 was admitted to the Royal Victoria Hospital on Oct. 15, 1958, com-

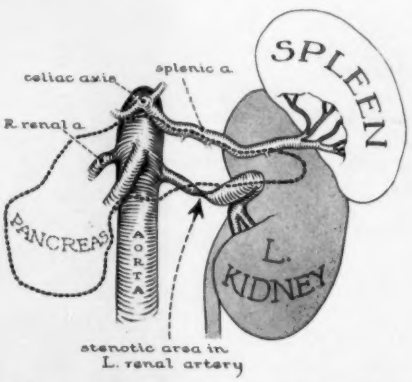

Fig. 4.—Diagram of left renal artery stenosis with poststenotic dilatation.

plaining of headache, pounding in the chest, and buzzing in the right ear for the past three months. His B. P. was 220/140. His I. V. P. was normal, with equal-sized kidney shadows. His fundi were Grade 2. An aortogram (Fig. 3) was first done and revealed a very large poststenotic dilatation involving the left renal artery. This was large enough to resemble an aneurysm. With this positive finding, differential excretion studies and the tetraethylammonium test did not appear necessary, and operation was performed on Oct. 20, 1958. Through a left thoracoabdominal incision the splenic artery was detached from the spleen, brought down and anastomosed end-to-side to the very large poststenotic dilatation in the left renal. This dilated portion occupied over half the length of the renal extending up to the point of its bifurcation making an end-to-end splenic to renal impossible. A hard plaque was present in the renal about 2 cm. from its origin, and a marked thrill was present in the poststenotic portion.

Postoperatively his symptoms immediately disappeared, and his B. P. progressively lowered from 160/104 on the first day to 124/80 on the sixth. He has been free of symptoms and normotensive since.

Comment

It appears without question that the ideal therapy in these cases of renal artery stenosis is to save the kidney and reduce the hypertension by renal revascularization. The slow development of this technique has been due to the difficulties in diagnosis and uncertainty as to the best method of revascularization. Scattered reports of a few cases so treated have appeared in the literature, but the techniques have varied. Poutasse [8] reports a case where a homograft was inserted from the aorta to the left renal to bypass a left renal stenosis. Freeman [9] has employed endarterectomy to remove the arteriosclerotic plaque in the renal artery. De Camp [10] has employed endarterectomy in two cases, excision of the stenosed area, with reanastomosis in one and splenorenal arterial shunt in two. The symptoms were relieved, and the B. P. either improved or returned to normal in all cases. Parton [11] reports one cure by end-to-side splenorenal shunt.

Owing to the uncertain future of arterial homografts, these should not be used. The same applies to plastic grafts, where the

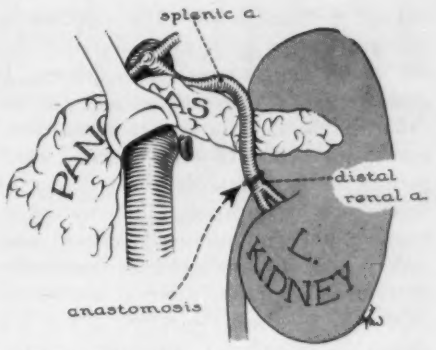

Fig. 5.—Diagrammatic outline of technique in operation performed on Cases 1 and 2.

failure rate in the smaller sizes prohibits their use. Autografts are ideal, and the splenic artery is readily available, especially for left-sided renal lesions. In our first two cases we removed the spleen but in the latter two we left it intact. The spleen appears to survive without its main arterial supply, and its preservation would seem indicated if feasible. In the case with bilateral renal artery stenosis, as has been reported in children, it would seem advisable to remove one kidney and revascularize the second.

The partial improvement in Case 1 could be explained by the extensive degree of arteriosclerosis he manifested with possible undemonstrated changes in the opposite

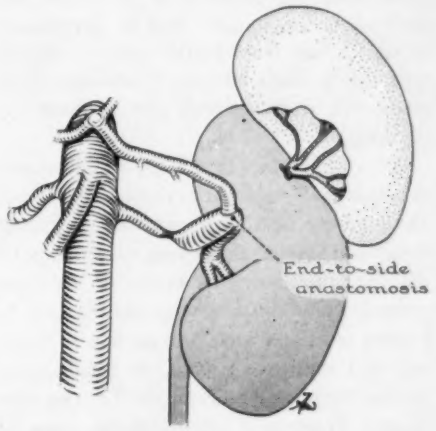

Fig. 6.—Diagrammatic outline of end-to-side anastomosis with preservation of the spleen done on Cases 3 and 4.

kidney or renal artery. The response to antihypertensive drugs after operation, but not before also suggests the ischemia is gone. A more likely explanation for the failure of the B. P. to drop to normal postoperatively is the 12-year duration, which permits diffuse arteriosclerosis to develop as in essential hypertension. The tetrathylammonium test postoperatively showed only a drop in B. P. It would have been better to do an end-to-side splenorenal anastomosis in this case because the splenic artery was shown to be affected by arteriosclerotic changes and possibly the repaired kidney is still not sufficiently vascularized. The failure in Case 3 is likely due to incorrect case selection with increased vascular tone being more of a factor than renal artery stenosis. At this point in our experience it would seem that definite well-demonstrated stenosis of the artery with poststenotic dilatation should be present before these cases are treated surgically. With the adoption of the Seldinger technique better aortography and therefore better case selection will be available.

We have been fortunate that all of our cases have shown left-sided lesions. However, at the moment of writing, a right-sided lesion will be admitted shortly and we plan to swing the splenic artery to the right after dissecting it down to its origin. An end-to-side anastomosis will be performed. If this is not feasible, the inferior mesenteric artery could be used. A complete high transverse incision should give adequate exposure.

Arteriosclerotic plaques are the commonest cause of renal artery stenosis. Other factors have also been reported, including congenital intimal thickening, coarctation of the abdominal aorta, aneurysm of the renal artery, syphilitic arteritis, subsequent to trauma associated with retroperitoneal bleeding, and encroachment on the renal orifice by the aortic thrombus in the Leriche syndrome. Freeman[12] reports three cases of sudden onset of hypertension following aortic endarterectomy where the renal orifice

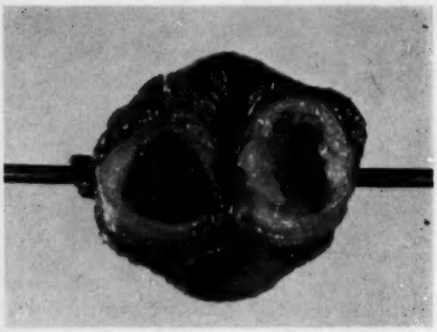

Fig. 7.—Resected specimen of renal artery from Case 2 with proximal arteriosclerotic stenosis on left and poststenotic dilatation on right of U-shaped specimen.

was inadvertently narrowed by removal of adjacent arteriosclerotic intima.

Summary and Conclusions

Four cases of renal artery stenosis with hypertension have been described where revascularization of the ischemic kidney was attempted rather than the previously employed technique of nephrectomy. Salvage of the relatively normal "ischemic" kidney rather than having the patient remain with one nephrosclerotic kidney is the rationale for the change in procedure. We believe renal artery stenosis as a cause of hypertension is much commoner than is now believed.

The selection of the appropriate case is somewhat difficult, but properly conducted differential renal excretion studies, the response to tetraethylammonium chloride, and, particularly, good renal arteriograms should allow proper selection.

Revascularization should be accomplished by autogenous arteries, the splenic being the best. End-to-side anastomosis is preferred to end-to-end, thus ensuring an addition to the already existing renal blood flow.

The etiology of renal artery stenosis is discussed along with alternative methods of revascularization.

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Addendum

The right-sided renal stenosis mentioned in the text was revascularized through a

long high transverse incision disconnecting the splenic artery from the spleen, dissecting it up to its aortic origin and passing it to the right through a tunnel dorsal to the pancreatic head. The patient's blood pressure has dropped from a preoperative level of 240/130 to 150/90 with marked improvement in her general condition.

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Carotid Artery Occlusion

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Extracranial vascular obstruction as a cause of cerebral ischemia is being recognized with increasing frequency. Carotid artery occlusion as a specific cause of neurologic deficits has drawn our attention since encountering our first case in June, 1956. We have now explored 15 patients suspected of having this ailment, and certain lessons learned seem worthy of report. Special attention will be directed to case selection and surgical management.

Tables 1, 2, and 3 summarize our experience with the 15 patients. The four patients in Table 1 have had no recurrence of neurological difficulties to the present time. That this definitely means patency of the artery cannot be proved authoritatively without postoperative arteriograms. Jackson and Fromm [1] and Gurdjian and Webster [2] have emphasized the occasional improved patient with angiographic evidence of obstruction not relieved by surgery. Figures 1 and 2 demonstrate the preoperative occlusion and postoperative patency of our first successful thromboendarterectomy. This patient has remained well for two years and eight months. Figures 3 and 4 are the preoperative and postoperative angiograms of Case 2 from Table 1. We have not been able to obtain postoperative angiograms on the third and fourth patients, but clinically the arteries are functioning.

Analysis of the eight patients in Table 2 strongly suggests the futility of surgical treatment for the patient whose neurological manifestations are already constant. Case 1 of this group had a complete right hemiplegia for two weeks before arteriography revealed the diagnosis. At surgery an atheromatous plaque at the carotid bifurcation, with an organizing thrombus extending into the internal carotid artery, was removed. The distal portion of the internal carotid artery pulsated weakly after the arterial repair. Although this vessel appeared to be patent, there was no improvement noted during the remaining three-week hospital stay.

The second patient, age 68, was admitted aphasic with right hemiparesis. She progressed into coma, and only then was an arteriogram performed. This study revealed a complete block of the right internal carotid artery. With use of local anesthesia, a large bifurcation plaque with recent thrombus extending into the internal carotid artery

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TABLE 1.—*Patients Improved After Surgery*

Case No.	Sex	Color	Age	Preoperative Symptoms and Duration	Operation Anesthesia	Result
1	F	W	49	Recurring right-sided weakness with speech difficulty — 1 yr.	Thromboendarterectomy General; hypothermia to 94.5 F.	No recurrence of symptoms
2	M	W	59	Intermittent weakness right arm; slight speech disturbance — 1 wk.	Thromboendarterectomy General; hypothermia to 91 F.	No recurrence of symptoms
3	M	W	62	Recurring right-sided weakness; frequent fainting episodes — 2 mo.	Thromboendarterectomy General; hypothermia to 92 F.	No recurrence of symptoms
4	F	W	53	Personality change 1 ½ yr.; right-sided weakness intermittent for 2 wk.	Thromboendarterectomy General; hypothermia to 89.5 F.	Rapid progressive improvement

Fig. 1.—Preoperative arteriogram of Case 1, Table 1, revealing almost complete occlusion of the internal carotid artery.

Fig. 2.—Postoperative arteriogram of Case 1, showing patent internal carotid artery.

was dissected free. This manuever required 11 minutes of arterial clamping, following which a good flow entered the internal carotid. Nevertheless, the patient continued her failing course and died 36 hours after surgery. Autopsy revealed extensive left cerebral encephalomalacia with an area of localized hemorrhagic extravasation.

The third patient, unimproved after surgery, exemplified the general nature of the

Fig. 3.—Preoperative arteriogram of Case 2, Table 1, showing incomplete obstruction at the carotid bifurcation.

Fig. 4.—Postoperative arteriogram of Case 2, revealing complete relief of original obstruction.

TABLE 2.—*Patients Unimproved After Surgery*

Case No.	Sex	Color	Age	Preoperative Symptoms and Duration	Operation Anesthesia	Result
1	M	C	42	Right hemiplegia; partial aphasia — 15 days	Thromboendarterectomy General; hyopthermia to 92 F.	Unchanged
2	F	W	68	Right hemiplegia; coma — 48 hr.	Thromboendarterectomy Local	Died 36 hours after surgery
3	M	W	59	Sudden left-sided paresis — 12 hr.	Thromboendarterectomy Local	Unchanged
4	M	W	37	Left hemiparesis — 19 days	Excision of redundant segments with anastomosis General; hypothermia to 92 F.	Unchanged immediately; gradual recovery in 2 mo.
5	M	W	62	Right hemiparesis — 5 wk.	Thromboendarterectomy General; hypothermia to 84 F.	Unchanged
6	M	W	63	Headaches; transient numbness left hand; 2 episodes blindness — 1 mo.	Thromboendarterectomy General; hypothermia to 83 F.	Complete paralysis left arm 12 hr. after surgery; gradual recovery over 7-wk. period
7	M	C	63	Aphasia; right-sided paralysis, partial — 48 hr.	Endarterectomy General; hypothermia to 88 F.	Immediate improvement; readmitted 12 days after discharge, in coma; died in 30 hr.
8	M	W	56	Numbness right side of face; slurring speech — 5 days; parasthesias — 3 mo.	Partial endarterectomy General; hypothermia to 88.5 F.	No change

atherosclerosis in many of our patients. This 59-year-old man was admitted for study and possible surgical treatment for intermittent claudication. Figure 5 reveals the atherosclerosis of the distal aorta and obstruction of the right external iliac artery. While in the hospital the patient had a sudden onset of paresis of the left arm and leg. There was a loud bruit over the right carotid artery. Figure 6 demonstrates the occlusion of the right internal carotid artery. Twelve hours after onset of neurological symptoms,

Fig. 5.—Aortogram of Patient 3, Table 2. Right external iliac artery is completely occluded.

Fig. 6.—Carotid arteriogram of Patient 3, revealing complete obstruction of the internal carotid artery just distal to the bifurcation.

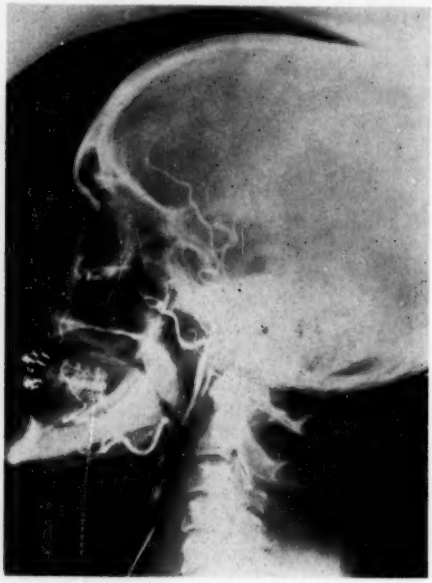
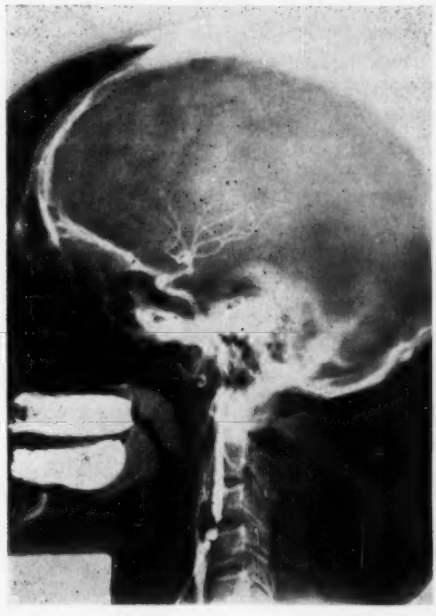


Fig. 7.—Arteriogram of Patient 4, Table 2, revealing coiled internal carotid artery.

a large calcified plaque with small fresh thrombus was removed from this artery. The patient walked from the hospital 18 days later, but weakness has continued in the left leg. Recently this man suffered a nonfatal coronary thrombosis.

The fourth patient, unimproved after surgery, was of special interest since the

Fig. 9.—Arteriogram of Patient 6, Table 2, revealing the partial obstruction distal to the bifurcation.



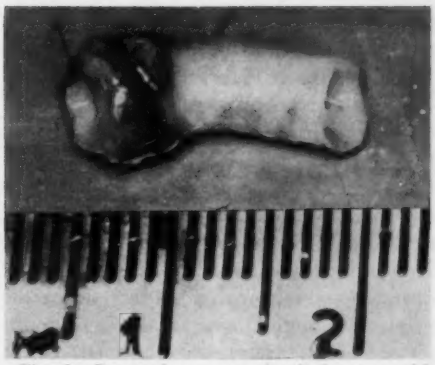


Fig. 8.—Resected segment of coiled artery with adventitia intact.

abnormal finding was probably of congenital origin. The coiled internal carotid artery, Figure 7, was also rotated to such a degree that at least two partial obstructions existed. This man, age 37, had a left hemiparesis for 19 days, preceded by two months of intermittent paresthesias on the left side. At surgery it was not possible to extend and anchor the redundant vessel in a permanent position that would prevent obstruction. Consequently, a segment, Figure 8, was excised and end-to-end anastomosis performed. This proved to be difficult since the proximal end of the vessel evidenced work hypertrophy and the distal end showed the thin wall of disuse atrophy. Dissatisfaction was our major feeling after surgery. This impression was confirmed one month later when an arteriogram revealed the vessel occluded at the site of anastomosis. Fortunately, collateral circulation must have been very good, for in two months' time this patient passed a physical examination for return to his job as a tool and die maker.

Case 5, unimproved, revealed a well-organized thrombosis on atherosclerotic plaques in the common, internal and external carotid arteries of the left side. This 62-year-old man had severe weakness of the right arm and leg for five weeks prior to surgery. There was no improvement following thromboendarterectomy.

Patient 6 had suffered two temporary blind episodes, transient numbness of the left hand, and severe headaches in the month

prior to admission. This patient appeared to be in imminent danger of a major stroke. The angiogram, Figure 9, revealed partial obstruction immediately distal to the bifurcation. With use of hypothermia, 83 F, the right carotid artery was exposed. The common carotid measured 8 mm. in diameter compared with 4 mm. for the external carotid and 3 mm. for the internal carotid. A well-organized thrombus extending 2 cm. into the common carotid artery from the bifurcation and 1.5 cm. distally into the internal carotid artery was removed. After incision closure, the pulsation seemed to be 60% to 70% increased over preincisional pulsation. Six hours after surgery the patient appeared quite well. Twelve hours after surgery a sudden major paralysis of the left arm and leg was noted. Over the next seven-week period the patient made a gradual recovery.

Case 7 was diagnosed angiographically as almost complete occlusion of the left internal carotid artery. This study was necessary to diagnose the cause of an aphasia and right paresis of 48 hours' duration. At surgery there was extensive atherosclerosis of the entire cervical carotid system on the left, and, although a good flow was obtained following endarterectomy, it was felt essential to keep the patient on anticoagulants for the remainder of his life. He was discharged improved in 14 days. Twelve days later he was readmitted in coma. The admission prothrombin level was 100%. This patient died 36 hours after admission, and autopsy revealed extensive thrombosis of the middle cerebral artery on the left.

Case 8 presented clinical signs of partial occlusion of the left internal carotid artery. Percutaneous arteriogram was unsuccessful. Open attempt at arteriogram revealed extensive occlusion of the common and internal carotid arteries. Four days later the carotid was explored, revealing an organized thrombus extending from a plaque at the aortic origin of the left common carotid distally into the internal carotid artery. From the neck incision it was impossible to open the obstruction at the aortic origin. A steady stream of blood from the superior thyroid artery passed around the carotid bifurcation into the internal carotid vessel. This had no doubt been the major source of supply to the internal carotid artery. Postoperatively, the patient has continued to have slurring speech and numbness of the right side of the face.

The three patients summarized in Table 3 were suspected of having carotid artery occlusion. The first case, a 43-year-old woman, had a sudden left hemiplegia at work. Arteriogram was thought to show internal carotid artery obstruction. Exploration of the artery, however, revealed a patent vessel but occlusion of the middle cerebral artery. The second patient had been having fainting spells of short duration. His arteriogram was considered to be a definite obstruction. However, open arteriogram revealed the percutaneous injections had on each of two occasions entered the external carotid artery. The patient's neurologic changes were diagnosed as hyperirritable cerebral foci.

TABLE 3.—*Suspected Cases of Carotid Obstruction*

Case No.	Sex	Color	Age	Preoperative Symptoms and Duration	Operation Anesthesia	Result
1	F	W	43	Left hemiplegia — 2 wk.	Exploration; arteriogram General	Error in diagnosis; middle cerebral artery occlusion; unchanged
2	M	W	55	Repeated episodes of fainting	Exploration; arteriogram Local	Error in diagnosis; probable hyperirritable focus; unchanged
3	M	C	49	None; carcinomatous mass at bifurcation	Resection mass and artery; vein graft	Good blood flow; died 8 weeks later of disseminated carcinomatosis

The third patient in Table 3 suffered from carcinoma of the buccal mucosa. He had previously had hemimandibulectomy and radical neck dissection on the left. Palpation on the right side revealed a tumor mass at the bifurcation of the common carotid artery. Since this mass was the only evidence of extension at the time, it was excised with a segment of the common and internal carotid arteries and a vein graft was anastomosed between the two ends. There was gross evidence of a functioning graft at surgery. Eight weeks after this procedure the patient was dead of widespread metastatic carcinoma.

These three cases have been classified as suspected carotid artery occlusions, and Patient 3 actually had occlusion. However, none had both carotid artery occlusion and neurologic abnormality.

Comment

Review of the case histories from Tables 1 and 2 indicates the patient who has not yet had paralysis has the more favorable prognosis. None of our patients with paralysis at the time of surgery received benefit from removal of the arterial occlusion. Warren and Friedman [3] have recently emphasized this point. Conversely, the patient with intermittent or recurring weakness or paresthesias had a favorable outlook.

Careful observation of the arteriograms in our series revealed greater occlusion of the internal carotid artery in the patient with paralysis. This is probably not a valid conclusion, however, since the extent of functioning collateral circulation has much to do with adequacy of cerebral circulation.

Lessons regarding case selection were learned from several patients in Table 2. In the future, patients with such advanced neurologic changes as present in Cases 1, 2, and 5 would not be explored. It is very doubtful that the patient with paralysis of more than a few hours' duration can be helped surgically, and each of the previously mentioned patients was in this category.

It is our opinion that the patient with an abnormally small internal carotid artery as well as the patient with extensive atherosclerosis should be maintained on therapeutic doses of anticoagulants after surgery. Cases 6 and 7 might have been salvaged had this plan been instituted and continued. This still leaves the majority of patients not requiring anticoagulant therapy after operation.

In our series, no patient undergoing thromboendarterectomy had his carotid artery occluded by clamps longer than 13 minutes. The actual periods of occlusion varied from 9 to 13 minutes. Bigelow [4] has stated that the oxygen requirement at 30 C is a little less than 50% of normal. In most instances our patients approached this temperature and we feel the use of hypothermia gave considerable protection to the ischemic brain.

Thromboendarterectomy appears to us the most logical surgical treatment because it requires the shortest period of complete carotid obstruction and is technically simple. The great majority of carotid artery occlusions are at the bifurcation, thus lending themselves to this approach. Occasionally, however, the common carotid artery may be so occluded with plaques that a bypass graft from the subclavian artery or aorta to the internal carotid artery is the necessary manuever. Lyons and Galbraith [5,6] recently reported use of this method with apparent success in five of seven cases.

Summary

Surgical experience in 12 patients with varying degrees of common or internal carotid artery occlusion has been analyzed. It is apparent that the patient with partial occlusion, manifesting transient neurologic deficits, has a much better prognosis and should therefore be considered for surgical relief at the earliest opportunity. Use of hypothermia reduces the surgical risk. Therapeutic doses of anticoagulants should be given whenever the internal carotid artery is unusually small or extensively athero-

sclerotic. The most direct surgical relief is afforded by thromboendarterectomy.

We wish to thank Drs. Gass, Simmons, and McGuire, neurosurgeons, who encountered all of these patients and performed the arteriograms.

14219 W. McNichols (35).

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DISCUSSION

ON PAPERS BY DRS. LUKE and LEVITAN AND BY DRS. SMATHERS AND SMATHERS.

DR. JOHN J. CRANLEY, Cincinnati: I would like to thank Dr. Luke for permitting me to read his paper, and I would like to congratulate him on his results.

Our experience is limited to three patients, and in none were we able to revascularize the kidney.

[Slide] All three patients were young males. All had a left-sided lesion. All had sudden onset of hypertension of less than six months' duration. The diastolic pressure was over 110 in each one, as Dr. Luke has mentioned.

The first shows what appears to be an excellent case: a localized area of stenosis in the left renal artery. We operated, assisting the attending urologist, and on exploration found the kidney to have a large mass at the upper pole. Neither the urologist nor I nor the pathologist could give an opinion as to whether or not this lesion was benign or malignant, so it was elected to remove the kidney. Unfortunately, sections showed that the lesion was merely a subcapsular hematoma, apparently caused by the needle we used in doing the aortogram. This patient has been well for one year.

[Slide] The second aortogram shows no filling of the renal artery. However, since the case was typical, an operation was performed and the renal artery was found to be stenosed but not completely occluded throughout its entire length. It was also involved in inflammatory tissue. This was believed to be due to a smoldering septicemia unrecognized at this time. Later a coagulase-positive Staphylococcus aureus was grown out of the blood stream, and pathologically the arterioles of the kidney showed inflammatory action, and the renal artery was involved in fibrous stenosis.

[Slide] The last patient, as you can see, has a very small renal artery bilaterally, and a very small aorta. This arteriogram was repeated and, except for the needles, the two arteriograms are superimposable.

At operation we found a very narrow terminal aorta that measured 1.5 cm. in diameter. The right renal artery was about 4 mm. in diameter and soft. The left was about 3 mm. in diameter and sclerotic. We opened it distally in the hope of performing a splenorenal arterial anastomosis, and found the intima pouting out just as in a sclerotic femoral artery. We were forced to do an endarterectomy, and were left with a thin-walled vessel about 3 mm. in diameter. We were unable to perform a successful arterial anastomosis with the splenic artery, and had to remove the kidney.

In summary, we have three patients with three different etiologies. The first was apparently sclerotic; the second was inflammatory, and the third probably was congenital, with superimposed atherosclerosis.

DR. D. EMERICK SZILAGYI, Detroit: Dr. Homer Smathers was kind enough to ask me to comment on his paper. I am very happy to do so, because I believe his presentation is a valuable contribution to an important subject.

From perusing the recent literature it is not difficult to get the impression that angioplastic procedures have a very wide applicability in the management of carotid arterial occlusive disease. I am afraid that this impression is not entirely correct.

Occlusive lesions affecting the carotid system can be classified, I believe, in three groups. Into the first group will fall those cases in which the obliterating lesions are located near or at the aortic arch. The involvement is segmental, limited, and usually multiple, affecting the other large arterial trunks, subclavian, innominate and vertebral.

The second group comprises the cases in which the diseased segment is at the bifurcation of the common carotid artery. These lesions are also rather well demarcated and sharply localized. Both these groups are generally well suited for angioplastic procedures.

However, most cases that we have seen belong in a third group, which is characterized by diffuse involvement of the internal carotid artery, the

occlusive process extending well into the cranial cavity. Attempts at surgical correction in these instances almost always fail. Dr. Smathers' series comprised mostly cases of this description.

I believe this report (which shows a good deal of courage, since one is always disinclined to talk about one's failures) has done a distinct service in emphasizing the limitations of this type of surgery, and particularly in pointing up the great necessity for careful case selection not only on grounds of the clinical findings but also with the help of bilateral, good-quality, serial angiograms.

Dr. Edgar S. Brintnall, Iowa City: My comments will relate to the paper by the Drs. Smathers.

In Iowa City, during the past three years, Dr. Maurice Van Allen and I have operated upon eight patients with atherosclerotic occlusion of the internal carotid artery. Our criteria for operation have been, first, a clinical picture consistent with the diagnosis; second, a significant reduction in retinal artery pressure on the side of the suspected occlusion as measured with the ophthalmodynamometer. A 20% to 25% reduction in pressure is consistent with the diagnosis.

We have found obstruction of the internal carotid in every explored case, with a significant lowering of the retinal artery pressure. The potential hazards of arteriography when the internal carotid is not obstructed have made us reluctant to use this diagnostic aid.

By omitting angiography we may have failed to recognize certain cases of partial carotid occlusion where the retinal artery pressures may be equal on the two sides or very nearly so. However, it is possible that in such cases the equality of retinal artery pressures may signify that flow is not reduced to the point where surgery to relieve partial obstruction is indicated.

We perform thromboendarterectomy under local anesthesia without hypothermia. When partial obstruction is encountered, a plastic tube bypass is utilized to avoid ischemia.

[Slide] This slide shows the exposure of the carotid bifurcation and the forceps point at the site of occlusion, which is very commonly at the carotid bifurcation.

[Slide] In this patient, as the obstruction was partial, a plastic tube bypass was put in place during the endarterectomy.

[Slide] This is a rather interesting surgical specimen of atherosclerotic material with thrombus which was removed from the bifurcation region.

[Slide] This last slide shows that the specimen reveals a marked occlusion of the internal carotid with atherosclerotic plaque material plus some recent thrombotic material, with an open external carotid.

In our eight patients our results have been quite similar to the Drs. Smathers. Two were improved; five were unchanged by the procedure, and one, who developed postoperative intravascular clotting, was made worse.

Dr. Frederick S. Cross, Cleveland: I was interested, when reading the abstract of this paper in the program, in how closely Drs. Smathers' experience paralleled ours, which is the combined experience of Dr. William Trowbridge, of Cleveland, and me.

[Slide] This slide illustrates that in our total experience of 17 patients, only 1 had the typical history of "stuttering paralysis" or "little strokes," or whatever name you might wish to use. The remaining patients had an out-and-out picture of a stroke which had occurred within 6 to 12 hours prior to the time that we saw them. Although this may be a selected series, since these are the patients who ultimately ended up with the surgeon, this slide further illustrates the high incidence of carotid artery obstruction in a group of 17 consecutive patients entering the hospital with a clinical diagnosis of a "stroke." You will see that 11 patients had complete or partial occlusion of the internal carotid artery, 2 had basilar artery thrombosis, 1 had intracerebral hemorrhage, and only 3 had negative arteriograms.

[Slide] This is the operative specimen from our first and best result, and the only patient in our experience with a true picture of so-called "little stroke."

[Slide] This is a picture very similar to the one one Dr. Brintnall showed, illustrating the endarterectomy specimen taken from the bifurcation of the common carotid with partial obstruction of the external as well as the internal carotid.

[Slide] As far as our results are concerned, they are not too good because the patients whom we operated on were not good risks. There were six who survived the procedure, and there were four deaths.

I would like to emphasize again at this point that these patients, with the exception of one, had entered the hospital with a full-blown picture of a "stroke." Some of them were semicomatose, definitely on the way downhill, and I am sure we did not help them, possibly speeding them on their course in certain instances.

[Slide] This shows the results in those patients who did survive the operative procedure. We had complete recovery in the one patient with the history of intermittent difficulty, which, of course, is the ideal type of patient to operate on. There was one patient who returned to work with a mild deficit; there were two who are capable of complete self-care, and the results of the remainder are as shown. One gratifying result was in a woman who had had the recent onset of an out-and-out stroke with paralysis and aphasia. We operated on her within about 12 hours, and she is now com-

pletely capable of taking care of herself, with no residual difficulty except for some dysphasia.

I think there is one thing to be learned from this experience, and that is that the results of surgery for carotid artery occlusions will be good only if the case selection is good. It is our feeling at the present time that in most instances only those patients with an intermittent picture of paralysis and associated symptoms should be operated upon. Those patients with an out-and-out stroke, even if they are seen within 6 to 12 hours, are for the most part not going to be helped by carotid endarterectomy.

DR. HOMER M. SMATHERS, Detroit: I wish to thank Dr. Brintnall and Dr. Cross for showing some of the specimens, which were practically identical with ones that we removed.

In some cases, however, a nice thrombus (and I am sure they had them, too) was on the ends of the plaques. Many of our medical conferees are strongly advocating anticoagulants for this disease. I believe that in the artery almost completely plugged with a plaque, containing a thrombus on top of it, the opportunity to perform endarterectomy will have far more to offer the patient having recurring attacks, than will the anticoagulant therapy.

Recent Advancements in the Treatment of Peripheral Arterial Embolism

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While treatment of an embolism of the peripheral arteries has within the course of the last 50 years evolved through the broad classic stages of desperate innovation and ingenious resort to every available means of therapy which are common to most medical emergencies, nevertheless the combination of surgical removal of the embolus at the earliest possible moment plus the prophylactic use of anticoagulant therapy has emerged as the soundest and most widely accepted method of treatment. Recent advancements concern themselves primarily with refinement and progressive application of these two approaches to treatment.

The compelling logic of surgical removal of an arterial embolus has stood the test of time. It is interesting that surgical removal of emboli was first suggested by John Hunter[1] in 1768. It was not until 1895, however, that an attempt was made to remove an embolus by Sabanejeff,[2] and it was 15 years later, after 14 attempts resulting in four amputations and 10 deaths, that the first embolus was successfully removed by Labey.[3,4] During the next 30 years, despite numerous successful embolectomies, the surgical management of arterial embolism did not reach maturity until anticoagulant agents became readily available to the medical profession.

Recent advances in the management of peripheral arterial embolism have derived from elaboration of the surgical and medical approach to therapy. Perhaps as a consequence of the rapid progress made recently in direct arterial surgery, surgeons have become more aggressive and no longer hesitate to perform multiple arteriotomies in an attempt to remove an embolus or a propagating thrombus. Medically, as a consequence of better recognition of the devastating effect of a propagating thrombus, heparin has been found useful as a preoperative prophylactic when operation is necessarily delayed and is widely used postoperatively, to be followed later by the prothrombin-depressant oral anticoagulant agents.

Despite these advances, however, arterial embolism remains an acute medicosurgical emergency of the greatest magnitude. Its gravity can be attested to by the fact that 40% of all the patients seen during the past six years with an arterial embolus died before discharge from the hospital. On the other hand, the fact that it has been possible to remove the embolus and restore arterial circulation in 88% of all those on whom an operation has been performed within six hours affords hope for continued substantial improvement in the future.

During the period from August, 1952, to December, 1958, 60 patients having 72 emboli were seen in practice. Fifty-seven emboli occurring in 48 patients were removed surgically. Seven patients having nine arterial emboli were treated by anticoagulant agents alone. And five patients were observed to whom no specific treatment was given. The sites of lodgment of 72 emboli are shown in Table 1.

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TABLE 1.—*Sites of Lodgment: Seventy-Two Peripheral Arterial Emboli*

Artery	No.	Per Cent
Aorta	3	4.2
Iliac	14	19.4
Femoral	41	57.0...80.6%
Popliteal	8	11.0
Axillary	1	1.4
Brachial	4	5.6
Ulnar	1	1.4
Total	72	100.0%

Thus 80% of the emboli in this series lodged in the aorta, or the iliac or femoral arteries. This approximates the observations of others.[4-9] * The morbid significance of this is emphasized by the fact that death, amputation, and severe incapacitation are to be expected following embolization in these critical sites if untreated; whereas the minority of emboli have lodged in less critical areas, such as the popliteal or in the upper extremities, where ischemic necrosis is less likely to occur following occlusion of an artery.

Origin of the Embolus

The heart was the site of origin of the embolus in 57 of the 60 patients in this series. In one instance the presumed site of origin was an abdominal aortic aneurysm; in another, a plastic valve in the proximal aorta, and in a third no source was apparent. Of the 58 patients with known heart disease, the etiology was arteriosclerosis in 47 patients; rheumatic fever in 7; a recent myocardial infarction in 3; and in 1 severe cardiac decompensation. Auricular fibrillation was present in 54 patients (90%).

Diagnosis

The diagnosis was apparent to the physician in charge of the patient in almost all instances in this series. Delay in treatment, when it occurred, was most frequently due to failure of the patient to call a physician at the onset of symptoms, or to the inability of the semicomatose or severely debilitated patient to signal for help. The history of a sudden onset of pain or numbness in the extremity followed by coldness, paresthesia, and paralysis is typical. On physical examination, a cadaveric lemon-yellow color arrests the attention. It is believed that this color has not been given the weight it deserves. It is the color of complete ischemia and is almost identical with the lemon-yellow hue seen on the autopsy table. The additional findings of mottling, coldness, absent peripheral pulsations, hypesthesia, and anesthesia confirm the diagnosis. In 90% of the patients in this study, auricular fibrillation was present.

Earlier in our experience, anesthesia and loss of position sense were considered to be the cardinal signs of irreversibility of the process. Further experience has proved this to be incorrect. At the present time, rigor of the muscles is considered to be a nearly ultimate sign, but even this is not absolute. In general, however, it may be said that prior to the onset of rigor, there is a good chance of saving the limb by clearing the major arterial pathways.

Sites of Lodgment

In the younger patient, the site of lodgment is invariably at the bifurcation of the major arteries. In the older patient, however, the embolus may lodge at a point of narrowing, especially in the adductor canal.

* In pondering over the fact that the incidence of upper extremity emboli in our series is somewhat less than that reported by others,[4-9] we recognized an element of statistical bias in this series. In a number of instances, perhaps as many as 10, during this same period of time we were consulted in hospital corridors or on the telephone about patients with upper extremity emboli. Since it has been our observation that most patients with upper extremity emboli do not come to amputation even when untreated, we have recommended anticoagulant therapy, especially in elderly patients, with a warning that surgical intervention be considered, if there was any deterioration of the extremity. Since we actually did not see these patients, they are not in our files and not in this series. Had they been included, the percentage of upper extremity emboli would have been greater and the percentage of lower extremity emboli correspondingly smaller.

Differential Diagnosis

The differential diagnosis between arterial embolism and acute arterial thrombosis may be difficult; however, in the latter case, excruciating pain, auricular fibrillation, or a history of myocardial infarction are usually absent. Femoroiliac thrombophlebitis is frequently mentioned as a major differential diagnosis. This should present no problem, because the distinctive pallor mentioned above is absent; there are no abnormalities of sensory and motor function, and there is swelling. Finally, should pulses be difficult to palpate because of the swelling, their presence can be detected by a standard oscillometer or an aneroid-type sphygmomanometer.

Time Interval Between Lodgment and Removal of the Embolus

The lapse of time between lodgment and removal of the embolus is a prime determinant of the outcome of treatment. After analyzing the world literature in 1923, Key [4] noted that no embolectomy had been successful more than 24 hours after lodgment of the embolus. He concluded that the prognosis of embolectomy was quite favorable during the first 10 hours, but that after this period chances of recovery deteriorated rapidly. He added the comment, however, that "no set time before gangrene occurs can be given; one must be prepared for great individual differences." Herein we concur. Several authors have noted an occasional successful outcome of embolectomy many hours after lodgment of the embolus. Warren and Linton [5] reported one embolectomy performed by McKittrick 60 hours after lodgment. Olwin, Dye, and Julian [10] reported six instances of late removal not only of the embolus itself, but also of the large distal propagating clot from arteries long after the commonly accepted period of surgical operability, one of them being four days after lodgment in the popliteal, and another six days after embolization in the axillary artery. More recently, Shaw,[11] Crawford and De Bakey,[12] and Krause and Cranley [13] have emphasized this point. Today, no patient should be denied operative treatment on the basis of elapsed time alone. As long as there is no obvious gangrene of the skin, profound rigor mortis of the muscles, or muscle necrosis as evidenced by swelling and induration over the muscle bellies, embolectomy should be undertaken. If a significant time lag between lodgment of the embolus and operation is unavoidable, it is believed that heparin therapy should be instituted preoperatively to forestall propagation of the thrombus until embolectomy can be performed. The following case illustrates this point. A 69-year-old white woman awakened at 7:30 a. m. and noticed that her legs were numb and that she was unable to stand. At 11 a. m., 2 p. m., and 6 p. m., she was given 50 mg. of heparin intramuscularly. A diagnosis of right common iliac and left common femoral embolus was made, and operation was performed at 9 p. m. Both the thrombus in the iliac artery and that in the femoral artery were nonadherent to the vessel wall, and there was practically no propagating thrombus. Since she awakened with numbness, one cannot say at what time precisely the emboli lodged; but the minimum time interval was 13½ hours.

Results of Treatment

Accurate analysis of therapeutic results may in some instances be difficult to obtain. In some cases, notably in the older age group, the patient may die from simultaneous lodgment of several emboli, one of them going to an inaccessible area. For example, a 71-year-old man was seen one hour after simultaneous lodgment of three emboli, one in the cerebrum, one in the right common iliac, and one in the left popliteal artery. The neurosurgical consultant was of the opinion that the patient might recover. Accordingly, the emboli were removed from the iliac and popliteal arteries. Although the circulation of the extremities was adequately restored, the patient never regained consciousness and died six weeks later. Obviously, the treatment of the emboli in

the extremities was successful, but the over-all treatment of the patient was not adequate to preserve life.

Another difficulty is posed by the fact that one may not know the circulatory status of the limb prior to the lodgment of the arterial embolus. For example, an extremely debilitated 86-year-old white woman was admitted with signs and symptoms of arterial embolism of the right common iliac artery. This was removed, with immediate restoration of the right common femoral pulse. No pulse could be palpated below the common femoral artery in either extremity. The left lower extremity appeared to be viable, and the right lower extremity was improving noticeably at the completion of the operation. It was assumed that this patient had chronic obliterative arterial disease of both lower extremities. Within a few hours, however, it became apparent that both lower extremities were deteriorating rapidly. She was returned to the operating room, and organized thrombi, as well as soft clots, were removed from the right superficial femoral artery at its origin and from the left at a plaque in the adductor canal. Both limbs survived, but the patient died nine days later from cardiac decompensation.

A third problem is presented by the actual presence of advanced arteriosclerosis prior to embolectomy. For example, a 70-year-old woman with diabetes mellitus was admitted with acute arterial occlusion in the right lower extremity. No pulse could be felt in either foot or in the right popliteal space. At operation, a small embolus was removed from the distal portion of a thickly sclerotic popliteal artery. Postoperatively, her limb became as warm as its opposite, and the discomfort gradually disappeared. Obviously, one cannot expect the return of pulsation in the foot of a patient such as this; but restoration of the circulation to its probable preembolus level must be considered adequate evidence of success.

Finally, difficulty is encountered in assessing the results of a limb in which the circulatory status is equivocal at the time of the patient's death. For example, a 73-year-old male patient after an embolectomy presented a limb that seemed to be holding its own for 24 hours and then began to deteriorate. Before it could be determined whether or not the limb would survive, the patient died.

In this report, the results of embolectomy are evaluated separately from the over-all mortality. If the limb was definitely viable at the time of death, the embolectomy is considered to be successful. If the limb was not unequivocally improved from its preoperative status, at the time of death, it is considered to be a failure and is added to the list of amputated limbs.

Table 2 lists the operative results related to the time interval between lodgment and removal of the embolus, and Table 3 lists the operative results related to the site of the embolus. Two of the three failures in the 48-72-hour category represent one 35-year-old parturient who had two emboli, one lodged in the right common iliac and the other in the left common femoral artery, that had been present for three days when the patient was referred for surgical treatment. At this time, the toes and distal por-

TABLE 2.—*Operative Results Related to Time Interval: Fifty-Seven Operations*

Time, Hr.	No.	Improved	Unimproved	% Improved
3- 6	25	22	3	88
7-12	13	11	2	85
13-24	14	8	6	57
25-36	2	1	1	50
48-72	3	0	3	0
Total	57	42	15	74%

TABLE 3.—*Operative Results Related to Embolic Site: Fifty-Seven Operations*

Site	No.	Improved	%
Axillary	1	1	100
Brachial	1	0	0
Aorta	2	0	0
Iliac	10	8	80
Femoral	39	29	72
Popliteal	4	4	100
	57	42	74%

tion of the feet were gangrenous; the legs were almost completely anesthetic, and it appeared certain that mid- or high-thigh amputations would be necessary. She was taken to the operating room, and after repeated flushing of the major arteries over a six-hour period all thrombi and clots were removed, so that the posterior tibial pulse was palpable at each ankle at the completion of the operation. Later it was possible to perform below-the-knee amputation successfully on each extremity. From the point of view of surgical treatment of arterial embolism three days old, this patient must be considered to have had a satisfactory result. However, because the patient's legs were amputated, she is listed in the amputation group, and, from a statistical point of view, she is considered a failure.

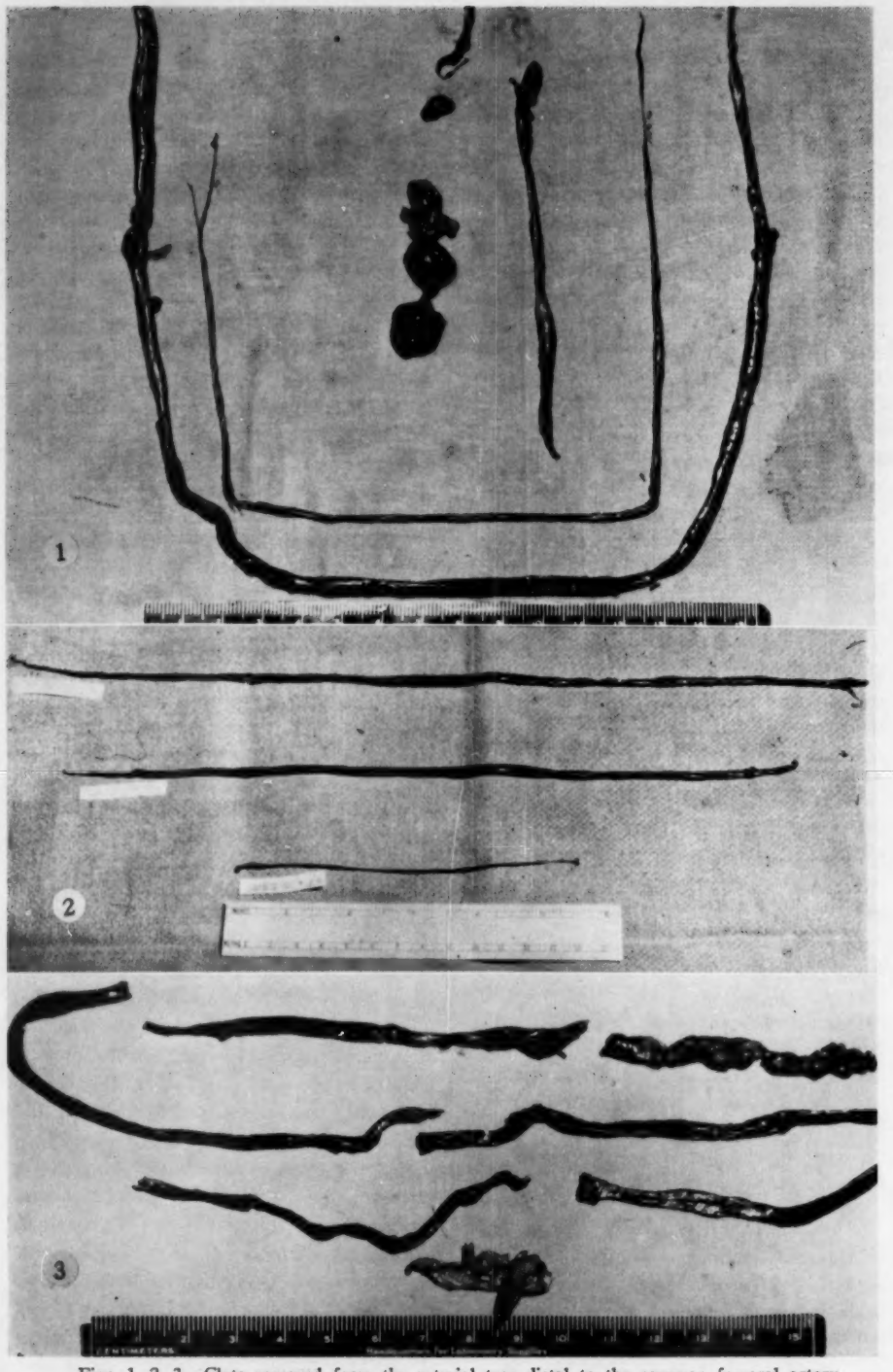
Recently, two femoral artery embolectomies have been performed in extremities in which rigor was present. In each case, it was possible to clear the artery and restore the arterial pulsations. However, both patients died postoperatively before it could be determined whether or not normal function had been restored to the limb.

Anesthesia

The majority of the patients reported here have been operated on under spinal anesthesia. When preoperative heparin is given, however, we have preferred general anesthesia because of the danger of bleeding following spinal tap. The specific anesthetic agent is of far less importance than the experience and proficiency of the anesthetist. Most patients with a major arterial embolus are poor surgical risks, and the availability of an experienced anesthetist is of the utmost importance. Two of the deaths reported in this series are believed to be properly classified as anesthetic deaths.

Operative Technique

A transabdominal approach to the distal aorta is preferred. The iliac arteries have been regularly exposed through a retroperitoneal lower abdominal oblique incision. The femoral artery is exposed by a longitudinal incision directly over its course, and the popliteal is approached through an incision on the medial aspect of the leg, just below the knee. As soon as the artery is isolated, distal and then proximal control is obtained, in order to prevent movement of the clot farther down the arterial tree, and to preclude hemorrhage when the artery is opened. The arteriotomy incision is made just below the embolus or over its most prominent portion. The arterial pressure will usually expel the clot proximally, and further manipulation is not necessary. Clots in the distal segment of the artery may be removed by a very gentle milking pressure with the finger. Repeated milking or heavy pressure is to be avoided. If good blood flow from the distal tree is not obtained following this maneuver, it may be possible to force out clots from the distal tree by rolling a tightly clenched fist up the thigh over the femoral artery. We have not used the Esmarch bandage technique as described by Keeley and Rooney,[14] but it would seem to be a reasonable procedure. If there is still not a good flow of blood from the distal tree, the artery is opened lower down and flushed out in a retrograde manner with saline solution. In three instances it was possible to remove a cast of the entire superficial, femoral, popliteal and posterior tibial arteries by this method (Figs. 1, 2, 3). Saline solution containing 10 mg. of heparin is used locally, to prevent thrombosis and to eliminate air from the artery prior to closure. Every effort is made to have hemostasis complete. And when this is possible, 25 mg. of heparin is given intravenously while the incisions are being closed. If hemostasis is not considered adequate, the use of heparin is delayed for from four to six hours. Oral anticoagulant therapy is started two or three days postoperatively, and when the prothrombin time is prolonged two to two and a half times normal, heparin is discontinued. It is our considered opinion that, once a major arterial embolus has been thrown off, anticoagulant therapy should be continued permanently, or at least



Figs. 1, 2, 3.—Clots removed from the arterial tree distal to the common femoral artery by the reverse flushing technique.

until several weeks after the cardiac rhythm has reverted to normal.

Emboli of the Upper Extremity

As mentioned above in the footnote, a statistical bias makes it difficult to draw any conclusions about our data on upper extremity emboli. While we have seen all patients about whom we were consulted with an aortic or lower extremity embolus, we have not seen a number of patients whose physicians consulted us about an upper extremity embolus. The two extremities on which an operation was performed had impending gangrene. One had a brachial artery embolus, and at the time of operation no blood flow could be obtained from the distal arterial tree. This patient was treated prior to the time that we were using the reverse flushing technique. The second patient had an axillary artery embolus, with no propagation of clot distally, but a clot 11.0 cm. long was removed from the proximal axillary and subclavian arteries (Fig. 4). There was complete restoration of pulsations in this extremity. Shumacker [15] has emphasized the point that upper extremities may be lost after arterial embolism. Our current opinion is that early embolectomy is certainly advisable whenever the patient is expected to return to active life, because, should the limb survive an untreated embolus, its function would be impaired. However, we prefer to treat the extremely debilitated patient with anticoagulant agents and to watch closely for evidence of deterioration of the extremity. If limb necrosis threatens, embolectomy is recommended at any age or physical state.

In this series, seven patients have been treated with anticoagulant therapy alone (Table 4). Since the majority of these emboli lodged in the upper extremity or the popliteal artery, it is not possible to draw conclusions about this method of treatment. One experience, however, seems worth reporting. A 57-year-old man was seen with all the signs and symptoms of a left common iliac artery embolism. The complete absence of pulsations in the limb was confirmed by oscillometric examination. The referring cardiologist believed the patient to be in such extremely poor condition that he implored us not to consider surgical treatment. The patient was placed on heparin therapy, and within 36 hours all the pulses of the extremity had returned. The oscillations were equal to the opposite extremity. The mechanism by which this remarkable improvement occurred is not clear.

TABLE 4.—*Results of Anticoagulant Therapy: Seven Patients, Nine Emboli*

Site	No.	Imp.	Unimp.	Amp.	Death
Iliac	2	2	0	0	0
Femoral	1	0	1	0	1
Popliteal	4	4	0	0	0
Brachial	2	2	0	0	0

Five patients who were seen with arterial embolus had no specific treatment. Four of these were terminal and died. One patient was seen four days after an aortic embolus, with gangrene to the midthigh bilaterally, and an elevation of temperature of 105 F. His legs were packed in ice for two days and then amputated through the proximal third of the thigh. The patient recovered and lived two years.

Despite the over-all success rate of embolectomy, insofar as survival of the limb is concerned (74%), the over-all mortality rate was 40%. The cause of death of all patients in this series is listed in Table 5.

Fig. 4.—Axillary artery embolus with proximal thrombosis.

TABLE 5.—*Arterial Embolism: Cause of Death in Twenty-Four Patients*

	No.	%
Congestive failure	14	58
Myocardial infarct	3	13
Multiple emboli	3	13
C. V. A.	3	13
Pulmonary infarct	1	4

Comment

The recent advances in surgical procedure, such as the use of multiple arteriotomies and the reverse flushing technique, are major contributions and have been justifiably well publicized. Of almost equal importance in our opinion is recognition of the value of heparin. Long advocated by Murray,[16-21] this drug is in a class by itself among the anticoagulant agents. Recent work by Williams[22] provides laboratory confirmation of this clinical impression. Preoperatively, heparin may extend the critical interval between lodgment and removal of the embolus by prevention of distal thrombosis and thus permit an operation to be performed successfully at a later time than would be possible without it. During the operative procedure, its local use is of immediate value, and postoperatively it offers some protection against clotting in the period of time during which it is necessary to control coagulation by prothrombin-depressant agents. Finally, although difficult to prove, it is our impression that some desperately ill patients with major arterial emboli may be treated with heparin alone, with the expectation that a certain per cent of the limbs will survive, despite the fact that the function may be impaired.

Conclusions

1. Early embolectomy is still the ideal treatment for peripheral arterial embolism.

2. If delay is unavoidable, aqueous heparin preoperatively may be of significant value.

3. The interval of time between lodgment and removal of the embolus is not an inflexible criterion of operability.

4. Permanent anticoagulant therapy is recommended after removal of an arterial embolus.

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DISCUSSION

DR. LOUIS G. HERRMANN, Cincinnati: I wish to support the principle of the early removal of emboli which obstruct the larger peripheral arteries. The use of an antithrombotic substance such as heparin is more logical and more efficacious in preventing secondary thrombosis than the use of any antiprothrombic substance which can be given by mouth. Secondary thrombosis in the vicinity of the lodgment of emboli in peripheral arteries often takes place in spite of adequate control by bishydroxycoumarin (Dicumarol) or similar antiprothrombic substances.

I also arise to object to the use of the words "Recent Advancements" in the title of Dr. Krause's paper. The treatment of peripheral arterial embolism as he has presented it was well demonstrated more than a quarter of a century ago. Einar Key performed the first successful peripheral embolectomy in 1912, and Frank Labey is reported to have successfully removed an embolus from the femoral artery at about the same time. Many previous unsuccessful attempts were made, but secondary thrombosis caused further occlusion of the arteries.

Most patients who develop peripheral arterial occlusion by embolism have associated serious myocardial damage and are poor surgical risks. In the late 1920's René Leriche followed the example of John Pemberton of the Mayo Clinic and removed clots lodged at the bifurcation of the aorta by inserting special clamps into the femoral arteries at the groin and thus made it unnecessary to approach the aorta by the transperitoneal or retroperitoneal route. In 1932 we modified this approach to clots at the bifurcation of the aorta by using the femoral arteries at the groin. With slight suction on one catheter and a mild pressure on the other, it is simple to dislodge a fresh embolus and have it either fragment or appear whole at the arteriotomy wound in the common femoral artery. This method is illustrated by the drawings in the above lantern slide. We have employed this procedure in 19 seriously ill patients and in 17 we were able to remove the clots successfully.

Many of you will remember that in 1939 Dr. Ravdin successfully removed an embolus from the bifurcation of the aorta through the femoral artery.

More recently Rollins Hanlon and his associates in St. Louis have had experience with this method and find it is superior to the transperitoneal or retroperitoneal approach to the bifurcation of the aorta in very ill patients. The use of heparin during the operation and for several days thereafter is of definite value in preventing secondary thrombosis.

The earlier an embolus can be removed, the less permanent damage to the intima of the large artery will result, and thus a better chance for permanent relief will be afforded by this operation.

DR. WILLIAM H. MEADE, Lansing, Mich.: Regarding the origin of the clot already mentioned, there is another one that occasionally occurs, and that is in the Leriche syndrome, where you have a clot at the bifurcation of the aorta. A portion of this clot may break off and go into the femoral or popliteal artery.

We have had two instances in which one patient had a carcinoma of the colon with metastases and developed, approximately two weeks after surgery, an avascularity of the lower extremity. We removed the clot. The patient subsequently died. He had no cardiac disease, no coronary disease. He had a clot at the bifurcation extending as far as the renal artery.

The aorta was nowhere near being completely occluded.

The second case was a woman who had a diverticulitis, who had generalized peritonitis, and who developed a left femoral artery syndrome. We removed the clot. The patient subsequently died. The only point of origin that we could find for her clot was at the bifurcation, where she had a Leriche type of syndrome. She was 54 years of age, and the man was 62.

DR. JOHN CRANLEY, Cincinnati: I would like to thank Dr. Herrmann for his scholarly advice, and Dr. Meade for his discussion.

It is our present belief that the less one does to the arteries, especially in an elderly patient with arteriosclerosis, the better. Our efforts to suck back clots by instrumentation from the femoral artery have been singularly unsuccessful. For this reason we prefer to get the widest and best possible exposure, and to remove the thrombus as gently as we can, without disturbing the artery any more than absolutely necessary. That is why we do not use the technique of inserting a catheter back into the aorta.

Sphincterotomy—An Evaluation of Its Physiologic Rationale

BEN EISEMAN, M.D.; W. H. BROWN, M.D.; S. VIRABUTR, M.D., and S. GOTTESFELD, M.D., Denver

Sphincterotomy has been advocated in the treatment of pancreatitis in order to minimize biliary reflux into the pancreas through a common outflow channel by diminishing resistance at the ampulla of Vater. This operation, which was first suggested by Archibald [1,2] and later thoroughly investigated by Colp, Doubilet, and Mulholland,[3-7] has had a varied degree of clinical acceptance. Experimental or clinical evidence of its efficacy in reducing the outflow resistance of the biliary tract over a prolonged period has been questionable. Judd and Mann [8] found that sphincter section in normal dogs and cats reduced the yield pressure in the immediate postoperative period but they made no measurements thereafter. Colp and Doubilet [3] in 1936 measured the pressures in the common bile duct of seven dogs, two to six months after cholecystectomy and sphincterotomy, and reported them to be less than the mean value found preoperatively in other animals, but they had not measured base-line preoperative controls, nor did they report serial determinations during the postoperative period. The true value of the procedure depends upon a prolonged sphincter incontinence and diminution in biliary outflow resistance into the duodenum.

This is a study of the effect of various types of sphincterotomy on ampullary resistance to flow in a series of 27 dogs and in 5 humans tested prior to sphincter section and for periods up to three months thereafter.

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From the Department of Surgery, University of Colorado Medical Center and the Denver Veterans Administration Hospital.

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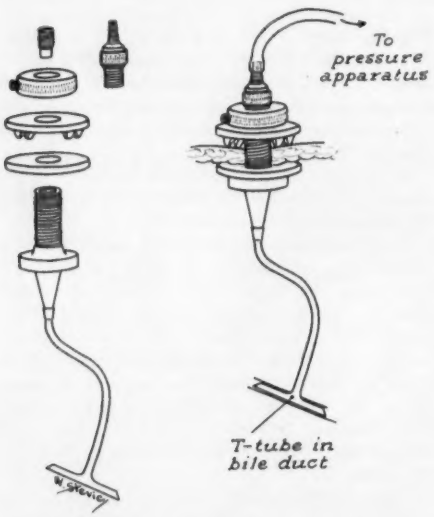


Fig. 1.—Nylon cannula used for measurement of yield pressure of common duct.

Methods

Cholecystectomy and T-tube intubation were performed in 27 adult mongrel dogs. The T-tube was fixed to the skin by a specially constructed nylon cannula as illustrated in Figure 1. Common duct yield pressures were measured on each animal at

TABLE 1.—*Summary of Animal Studies Showing Types of Sphincterotomy Employed*

Group	Type of Sphincterotomy	No. of Animals
I	Single-cut sphincterotomy	7
II	Double-cut sphincterotomy	6
III	Quadrant excision sphincterotomy	8
IV	Splinted single-cut sphincterotomy (Long-armed T-Tube)	6

the time of operation and at least twice weekly for two to three weeks thereafter in order to obtain a presphincterotomy base line in each animal.

The animals were divided into four groups as shown in Table 1. The seven animals in Group I underwent a single-cut sphincterotomy by incision of the papilla and superior margin of the sphincter and its intramural fibers for a distance of 1 cm. A patulous opening was thereby achieved, as evidenced by a wide gush of saline from the common duct upon T-tube irrigation and an immediate reduction in the yield pressure. Those in Group II had the sphincter sectioned in two places (double-cut sphincterotomy) 90 degrees apart, and in Group III, an entire quadrant of the sphincter was excised. In Group IV a long-armed Cattell T-tube was passed through a single-cut sphincterotomy and was left in place six to eight weeks prior to replacement with a short-armed T-tube. Resistance to common-duct flow in the latter group was measured for 3 weeks following cholecystectomy as a base line, and again for 6-10 weeks following removal of the Cattell tube 6 weeks after sphincterotomy.

Clinical.—Resistance of the sphincter was similarly measured immediately before and serially for at least 10 weeks after sphincterotomy in five patients with fibrosed, gallstone-obstructed, and spastic sphincters.

Methods of Measurement.—Measurement of resistance to flow from the common duct expressed as the pressure sufficient to initiate free flow of fluid into the duodenum is termed the yield of free-flow pressure. All measurements were made on fasting, unanesthetized animals lying quietly on the table, free from surrounding distractions. The level of the porta hepatis was used as the base line and the mean of 10 measurements made at 15- to 30-second intervals used as the yield pressure in subsequent calculations.

In Group II the sphincter was challenged by the gradual (5 cc. in 15 seconds) injection of saline into the common duct T-tube, using a 20 cc. syringe (Fig. 2) as previously described.[9] The point at which the manometric pressure suddenly dropped as fluid entered the duodenum was taken as the yield pressure. Although the initial reading occasionally was slightly higher (±3 cm. saline) than subsequent determinations, the yield pressures in any experiment have varied less than 1.5 cm. of saline.

The second technique used in Groups I, III, and IV for bile duct pressure measurements is similar to that described by Doubilet,[8] and consists of the gradual infusion (24 drops per minute) of saline into the T-tube from a Murphy drip apparatus elevated 64 cm. above the porta hepatis (Fig. 3). Measurements of the yield pressures were as described with the first technique. Pressures thus recorded were similar to those previously described by others,[6,10-12] and with but a mean variation of 6 mm. of saline were approximately 18 cm. lower than when measured by the syringe technique.

Free-flow or yield pressures were thus recorded in each animal at weekly intervals three times prior to sphincterotomy; at the time of laparotomy, immediately after opening the duodenum, immediately after sphincter section, and after closing the laparotomy incision. Postoperative measurements were made daily for a week and thereafter at weekly intervals for six to eight weeks.

The common duct yield pressures have been measured in five patients before and after single-

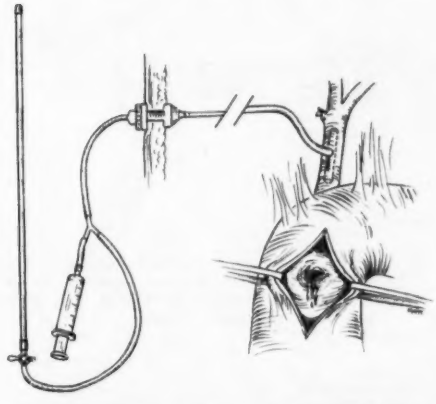


Fig. 2.—Syringe method for measuring yield pressure of sphincter in previous experiments and in Group II.

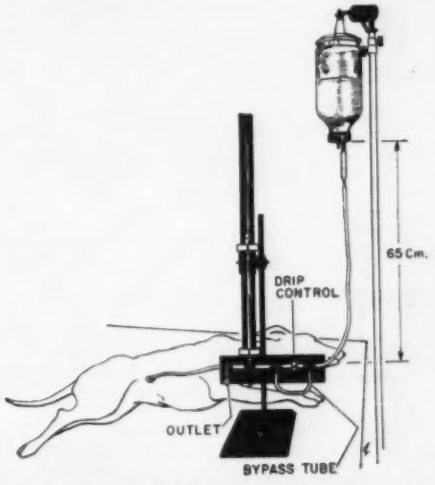


Fig. 3.—Constant-drip method for measuring yield pressure as utilized by Doubilet.

TABLE 2.—*Summary of Patients in Whom Yield Pressures Were Studied After Sphincterotomy*

Patient No.	Indications	Type of Sphincterotomy
1	To facilitate common duct exploration	Single section
2	Stenosis of sphincter (fibrosis)	Single section
5	Multiple common duct stones and "spastic" sphincter	Single section
4	Gallstone impacted at ampulla	Single section
3	To facilitate removal of common duct stones	Single section

cut sphincterotomy. In each case the second (continuous drip) technique was used for pressure measurement. Pressures were recorded after cholecystectomy but before sphincterotomy; and after sphincter section before duodenal closure. Postoperatively measurements were made every other day for 10 days and at weekly intervals thereafter. Details of the indications for choledochostomy and sphincterotomy are indicated in Table 2.

Results of Animal Experiments

Group I. Single-Cut Sphincterotomy.—Figure 4 illustrates the yield pressure response in dogs following a single-cut sphincterotomy. Immediately after sphincterotomy, the yield pressure fell markedly whether measured with the duodenum open or closed, but manipulation of the duodenum consistently caused an increase in yield pressure due to spasm of the duodenal musculature around the terminal portion of the common duct. In the immediate postoperative period and for three to four days thereafter the yield pressure was elevated, owing to edema at the operative site, but characteristically fell below preoperative levels by the end of the first week. During the ensuing four to six weeks the pressure gradually climbed to and often above preoperative levels. It is this return of sphincter tone that is of main interest in this study.

Group II. Double-Cut Sphincterotomy.—The yield pressures of this group are illustrated in Figure 5. The pattern of pressure changes is similar in all respects to that of

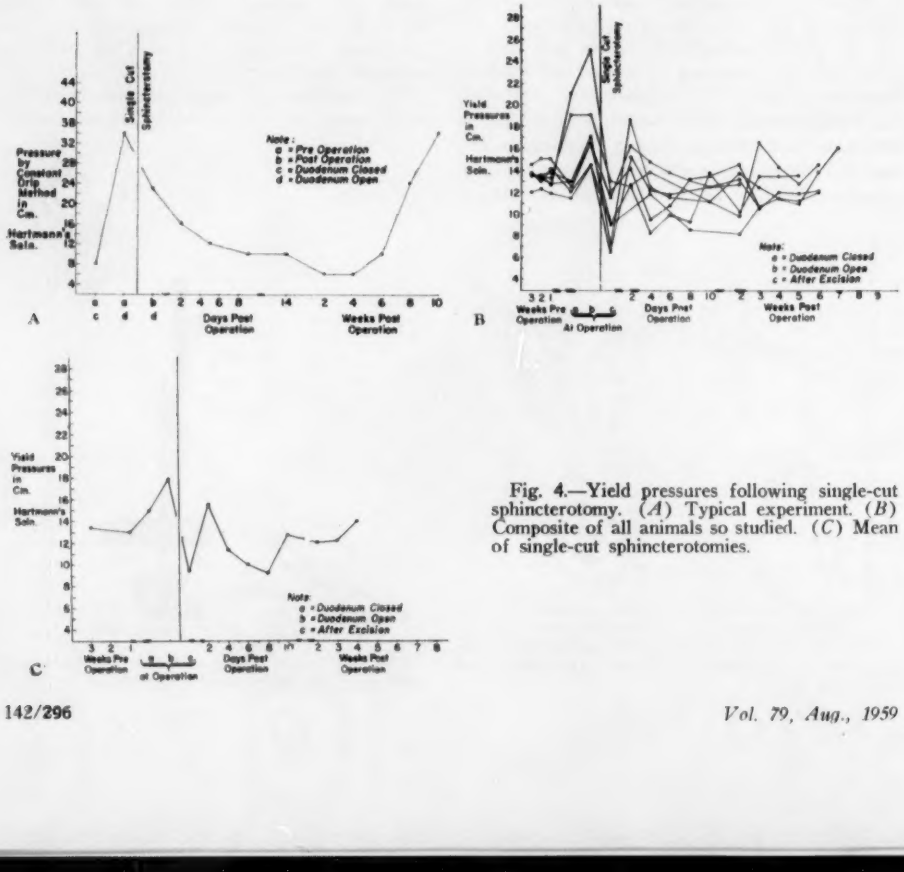
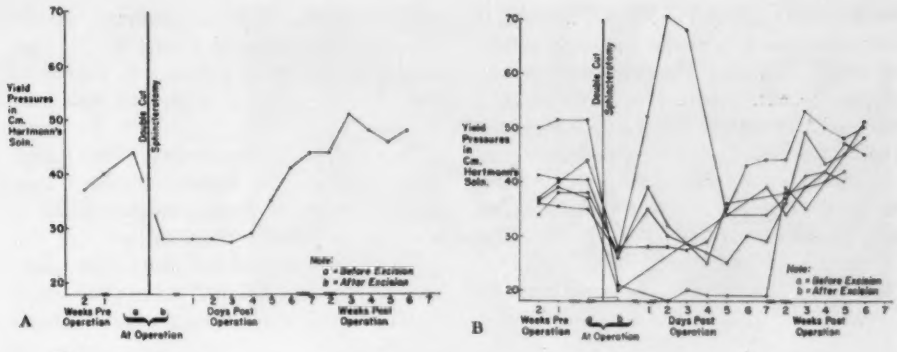


Fig. 4.—Yield pressures following single-cut sphincterotomy. (*A*) Typical experiment. (*B*) Composite of all animals so studied. (*C*) Mean of single-cut sphincterotomies.



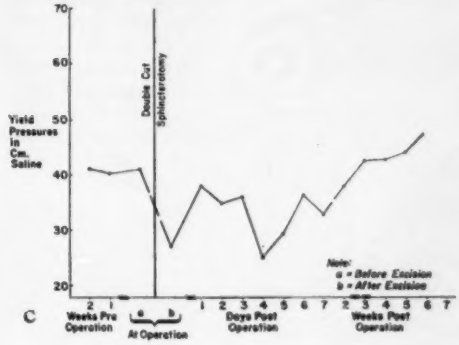
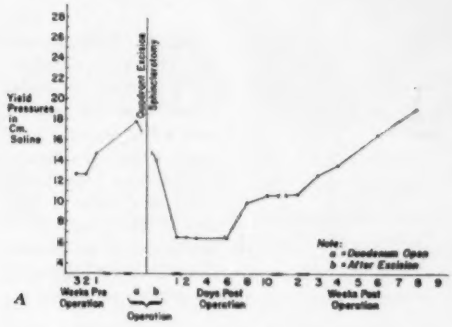
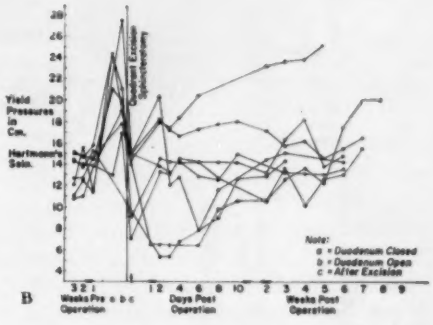


Fig. 5.—Yield pressures following double-cut sphincterotomy. (*A*) Typical experiment. (*B*) Composite of all animals so studied. (*C*) Mean of double cut sphincterotomies.





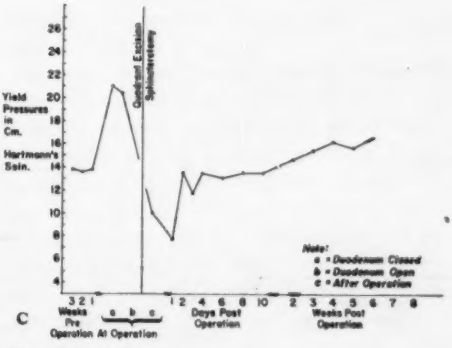


Fig. 6.—Yield pressures following quadrant excision sphincterotomies. (*A*) Typical experiment. (*B*) Composite of all animals so studied. (*C*) Mean of quadrant-excision sphincterotomies.

the single-cut group (Group I), namely, an immediate fall in pressure following sphincter section; a rise in free flow pressure during the edema period postoperatively; a fall to levels below this preoperative base line by the end of a week, and then a gradual return to or above preoperative levels in the four to six week period thereafter. Double section of the sphincter of Oddi, like single section, is only temporarily effective in reducing ampullary resistance.

Group III. Quadrant Excision.—The results of avulsion of a quadrant of the sphincter are shown in Figure 6. This response of the yield pressure is similar to that found in other types of sphincter section.

Grouy IV. Sphincterotomy Plus Long-Armed Cattell Tube Splint.—Figure 7 illustrates free flow pressure measurements in animals in which dilatation of the cut sphincter was assured for six to eight weeks with a long-armed Cattell tube, after which measurements were taken through a short-

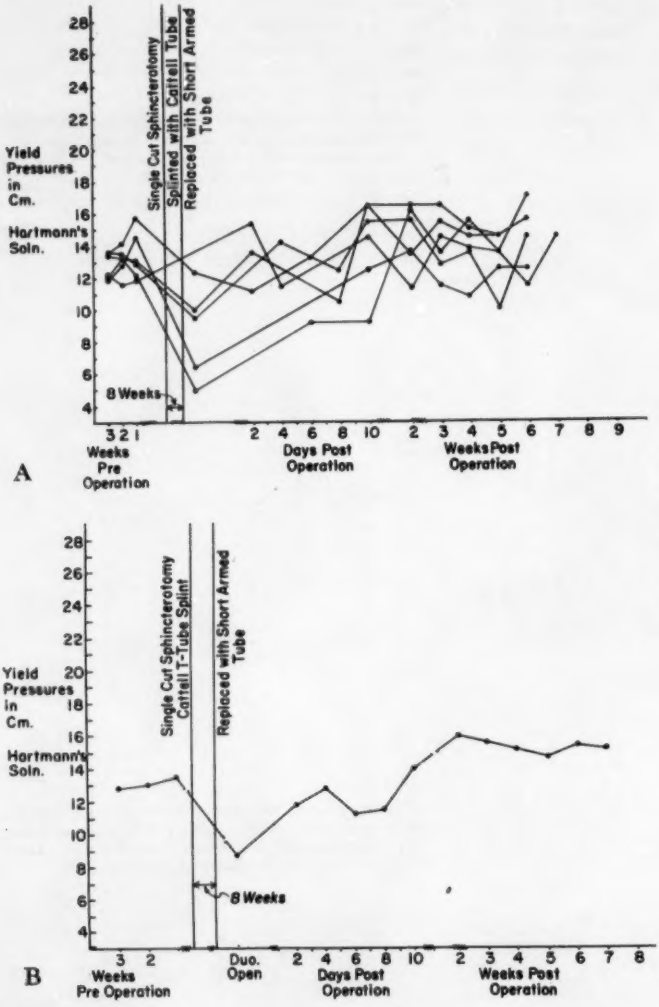


Fig. 7.—Yield pressure following single-cut sphincterotomy followed by six weeks of splinting with a long-armed Cattell tube. Pressure measurements begun immediately after shortening of long arm of the T-tube. (*A*) Composite of all animals so studied. (*B*) Mean of all animals so studied.

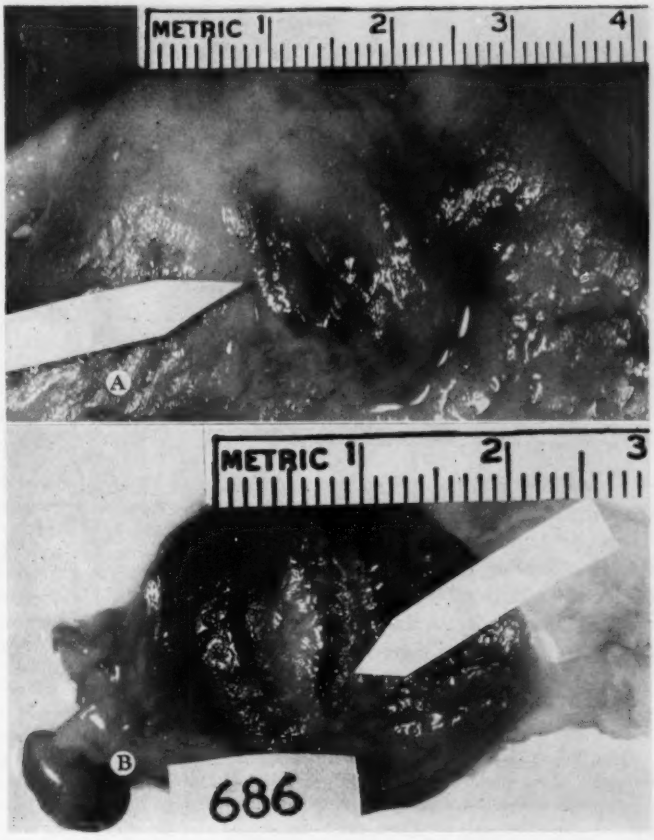


Fig. 8.—Gross appearance of dog ampulla. (*A*) Immediately after quadrant excision, showing widely patulent orifice. (*B*) Six weeks after quadrant excision, showing narrow aperture healed by scar.

armed T-tube replacement. Immediately after removal of the Cattell tube, the ampulla was patulous and resistance to flow minimal. Within four to six weeks resistance returned to presphincterotomy levels, indicating that six weeks of postsphincterotomy splinting did not alter the pattern of sphincter response from that found in the other groups.

In these studies it was found that error in the measurement of biliary tract yield pressure could occur from a variety of sources. Excitement of the animal, tonic or peristaltic waves in the duodenum occurring spontaneously or following operative trauma, a blood clot in the biliary tract, or a kink in the T-tube all could produce abnormally high readings. Immediately following sphincterotomy, edema and spasm of the surrounding duodenal musculature could appear so quickly that but one or two accurate readings could be made before spasticity of the duodenal wall excluded further accurate measurements.

Pathology.—Immediately after sphincterotomy, by whatever method, fluid flowed with minimal resistance in a wide flat stream through the patulous sphincteric opening. Six weeks thereafter the ampulla was contracted, and fluid forced through it assumed a thin stream of high trajectory. The gross appearance of typical, sectioned and scarred sphincters are illustrated in Figure 8.

Microscopic examination of these sphincters six weeks after operation consistently showed that the gap in the circular fibers had been spanned by a thin fibrous bridge

Fig. 9.—Microscopic appearance of dog sphincter of Oddi six weeks after single-cut sphincterotomy, showing scar tissue bridging the muscular defect and uniting the edges of the circular sphincter.

of scar tissue which restored continuity of the normal circular sphincter fibers (Fig. 9). These gross and microscopic findings of sphincter healing correlate with the return of sphincter action as reflected in an increasing resistance to free flow from the common duct into the duodenum.

Human Cases of Single-Cut Sphincterotomy

CASE 1.—A 56-year-old man who had a sphincterotomy to facilitate exploration of the terminal common duct, which was packed with stones. Figure 10 illustrates the free-flow pressures in the six weeks following operation and demonstrates the return of resistance to biliary tract drainage to presphincterotomy levels.

CASE 2.—A 60-year-old man who was found at laparotomy to have jaundice on the basis of a small, fibrosed sphincter which prevented passage of a No. 3 Bakes dilator. His gallbladder and common duct were acalculous. Following transduodenal section of his sphincter, the common duct yield pressure fell as illustrated in Figure 11, and remained depressed for more than two weeks. By the end of five weeks, however, sphincter resistance was once again elevated.

CASE 3.—A 58-year-old woman who had a sphincterotomy to facilitate removal of common duct stones. The yield pressure (Fig. 12) illustrates a return of ampullary resistance in the postoperative period.

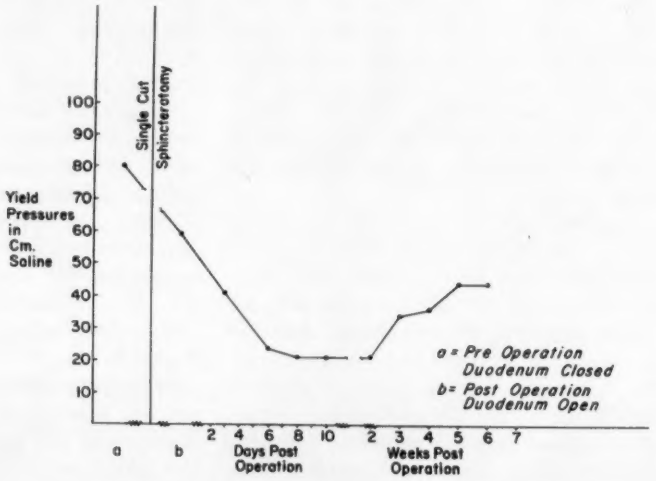


Fig. 10.—Human Case 1.

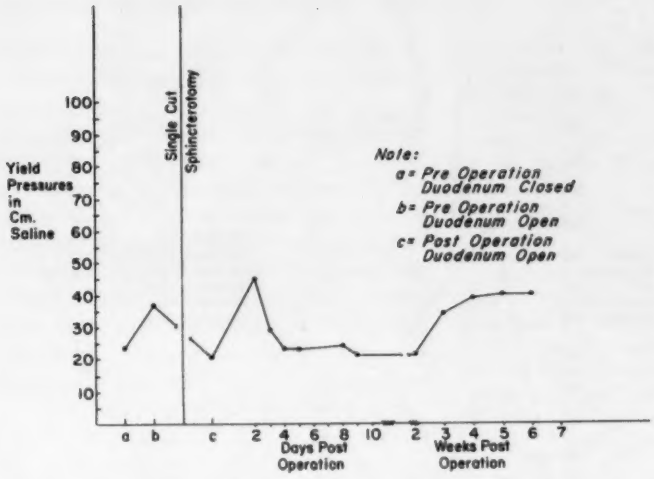


Fig. 11.—Human Case 2.

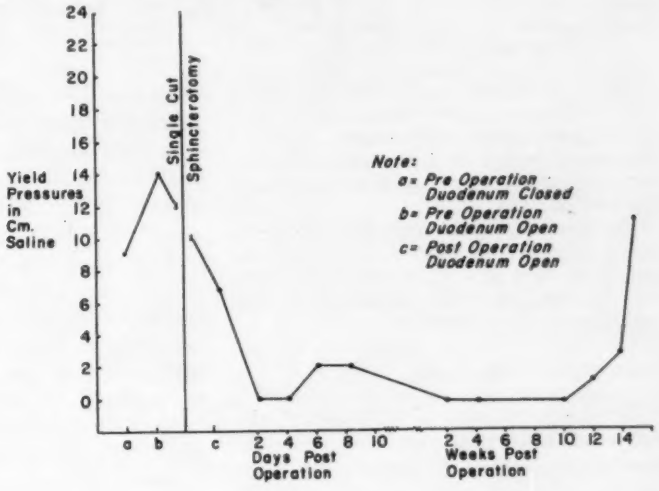


Fig. 12.—Human Case 3.

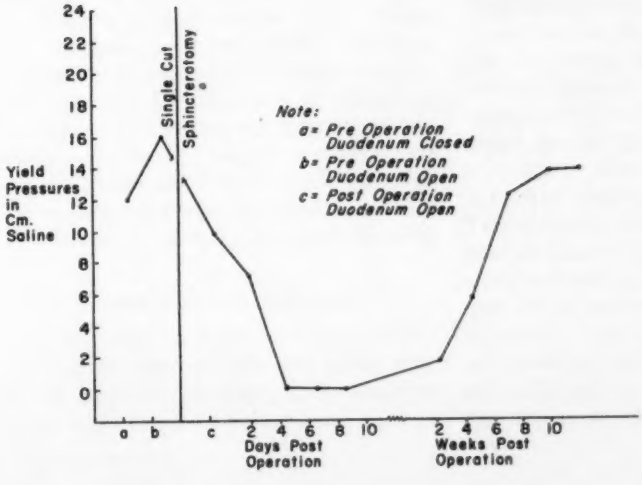


Fig. 13.—Human Case 4.

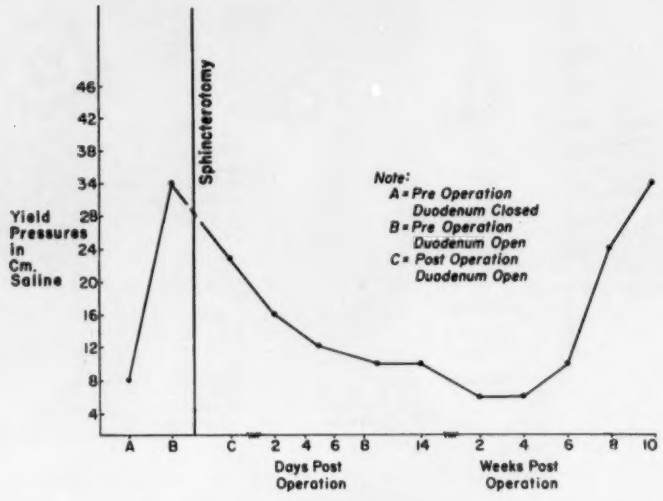


Fig. 14.—Human Case 5.

Case 4.—A 62-year-old white man who underwent sphincterotomy in order to facilitate removal of a gallstone impacted in the ampulla. Figure 13 illustrates the gradual return of resistance to biliary tract emptying that occurred in the six-week period following operation.

Case 5.—A 72-year-old white man who needed sphincterotomy for removal of a large gallstone impacted in the ampulla. Postoperatively ampullary resistance was minimal but gradually returned to normal, as shown in Figure 14.

Comment

There are two muscular components of the ampullary region that affect the free-flow pressures from the common bile duct: The first is that of the circular fibers of the sphincter at the ampulla; the second that of the muscle fibers spiraling around the duct in its intramural course through the duodenum.[13] Leuth [14] estimates that the sphincteric fibers in the ampulla of the dog account for but one-third of the total resistance to flow. In man the circular fibers at the terminal portion of the duct predominate,[13] and their section might be expected to exert a more profound effect on free-flow pressures than a similar procedure in the dog.

In evaluating sphincterotomy, great care must be taken to incise the sphincter no more or less than 1 cm., so that all of the circular fibers are clearly separated, yet damage to the duodenal wall and periductile pancreatic tissue is avoided. Sphincterotomy thus performed avoids inflammation and ultimate scarring around the biliary outflow tract. Such precautions were observed in this study.

A principle that is fundamental to surgery of any muscular sphincter is that a single transverse section does not produce incontinence. In light of the findings in this study, this principle is equally applicable to the sphincter of Oddi. Microscopic examinations of these sectioned sphincters show that continence returns by means of a fibrous contracture between the circular muscle fibers separated by the operative procedure. More extensive (double) section, or avulsion of a portion of the sphincter produces more scarring but does not apparently alter the pattern of circumferential sphincter repair. Even temporary splinting of the severed and dilated sphincter over a Cattell tube did not change the ultimate return of sphincter continence.

Summary and Conclusions

The pattern of yield or free-flow pressure within the common duct has been determined in a series of 27 dogs and 5 humans for a period of six to eight weeks

following various types of sphincterotomy.

Immediately following single-cut, double-cut, and quadrant resection of the sphincter of Oddi, resistance to fluid flow into the duodenum is minimal. Although edema at the operative site produces obstruction for a few days, yield pressures are reduced markedly by the end of the first postoperative week. During the ensuing four to six weeks free-flow pressures gradually return to or above normal preoperative levels. This pattern of response also occurs after removal of a long-armed Cattell T-tube used as a temporary splint after sphincterotomy.

Microscopic examination of the sphincter six weeks after its section shows an intact circular muscle with a fibrous scar uniting the cut or avulsed ends of the sphincter.

It is concluded that sphincterotomy is ineffective in permanently lowering resistance to fluid flow through the ampulla of Vater, and that this may in part account for the ineffectiveness of this procedure noted by so many in preventing recurrences of clinical pancreatitis.

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The Diseased Cystic Duct Remnant

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Cholecystectomy for chronically inflamed gallbladders with calculi provides an 85% to 90% satisfactory result. This high rate of amelioration in patients with chronic cholecystitis and cholelithiasis may be increased by the surgeon's technical "know how" in dissecting out the cystic duct to its junction with the common duct in preparation for total cholecystectomy. The purpose of this paper is to present a private practice series of cases of remnant cystic duct as a cause of postcholecystectomy symptoms and to review the literature on the subject.

The first surgical approach to the removal of gallstones was performed by Bobbs [1] in 1867, when he did a cholecystotomy on a living patient. Since that time cholecystostomy has been used and nearly abandoned in favor of the more curative procedure of cholecystectomy. As this latter procedure was generally adopted an appreciable number of patients began to haunt their surgeon because of persistence or recurrence of symptoms. The 10% to 15% incidence in these patients brought about the recognition of the postcholecystectomy syndrome. Beye's [2] monumental report in 1936 demonstrated 14 cases of "re-formed gallbladder" out of 66 cases showing symptoms after cholecystectomy. He concluded that symptoms were caused by this remnant cystic duct, and that the primary biliary surgery had been ineffectual in ablation of the disease. Peterson,[3,4] in analyzing his cases, stated that a history of jaundice after gallbladder surgery speaks more for a "re-formed gallbladder" than intrinsic pathologic changes in the common duct. He stated that preoperative diagnosis of this lesion is rarely logical, but it must be considered when symptoms recur or persist after previous cholecystectomy. Since the reports of these two authors appeared in the American literature, there have been additional case records presented, bringing the total now to approximately 200 cases showing a high rate of cure by surgical excision of the cystic duct remnant. Gagliardi and Gelbach [9] wrote that this condition is sufficiently rare that differential diagnosis is inadequate.

Although the "re-formed gallbladder" produces symptoms which are very similar to those of the original cholecystitis, the number of cases reported is few compared to the total number of operations on the biliary tract. This is indicated by the number of cases reported as shown in Table 1. When the surgical diagnostician sees a patient with a history of having had a cholecystectomy and presenting gallbladder symptoms, he is disarmed at once and seeks other explanations for the symptoms. Perhaps this explains why more patients are not operated on and reported.

TABLE 1.—*Summary of Cases of Remnant Cystic Duct*

Author Reporting	Date of Report	No. of Patients
Beye [2]	1936	14
Peterson [3,4]	1941-1946	42
Gray & Sharp [11]	1943	44
Miller [12]	1945	2
Bauer [13]	1951	1
Garlock & Hurwitt [14]	1951	30
Weingarten [15]	1951	1
Livingston & Livingston [16]	1952	1
Morton [5]	1954	20
Coulter [17]	1954	7
Glenn & Johnson [7]	1955	35
Grimes & Redd [18]	1955	3
Author's series	1958	14
Total		214

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TABLE 2.—*Preoperative Data*

Patient	Age	Sex	Original Surgeon's Classification	Primary Diagnosis	Date of First Surgery	Duration of Present Symptoms
1	47	F	Gen. Pract., little surg. training	Unknown	1918	11 years
2	65	M	Gen. Pract., self-taught surgeon	Unknown	1928	20 years
3	66	F	Gen. Pract., self-taught surgeon	Unknown (no stones)	1932	20 years
4	58	F	Gen. Pract., self-taught surgeon	Fibrinopurulent (no stones)	1945	6 to 7 years
5	44	F	Gen. Pract., self-taught surgeon	Chr. cholecystitis (with stones)	1945	12 years
6	30	F	Gen. Pract., no surg. training	Chr. cholecystitis (with stones)	1952	Continued
7	63	F	Surgeon, self-taught	Strawberry gallbladder	1952	Continued
8	48	F	Osteopathic Physician, training unknown	Unknown	1954	Continued
9	52	M	Surgeon, self-taught	Unknown	1954	Continued
10	66	F	Gen. Pract., self-taught surgeon	Unknown	1935	3 years
11	54	F	Gen. Pract., some surg. training	Unknown	1930	2 to 3 years
12	58	F	Gen. Pract., self-taught surgeon	Unknown	1933	25 years
13	69	F	Gen. Pract., some surg. training	Chr. cholecystitis (with stones)	1928	Recurrent 30 yrs.
14	41	M	Osteopathic Physician, training unknown	Chr. cholecystitis (stones ?)	1947	Continued

Cause of Symptoms

Some authors have thought that anatomical variations of the cystic duct with its incomplete removal may be responsible for symptoms. Morton[5] has considered that lack of contractility, together with the valves of Heister, gives rise to stasis and stone formation. This condition may then invite infection or result in chronic inflammation of the residual duct that may influence the motor function of the sphincter of Oddi. Womack[6] noted the presence of neuromatous nerve endings about the ducts to account for the postcholecystectomy symptoms. Glenn and Johnson[7] showed that most of their 35 patients were ward cases. Only three of their cases were found on the private service. This would seem to indicate that the experience of the surgeon has something to do with the symptoms which may continue or recur after gallbladder surgery. This point is borne out as shown by my classification of the technical surgeons of the primary biliary tract procedures in this series as indicated in Table 2. Hicken et al.[8] stated that continuation of symptoms following cholecystectomy may be due to three fundamental causes: first, incorrect preoperative diagnosis; second, residual hepatic disease; third, incomplete surgery. Beye[3] considered that dilatation of the "re-formed gallbladder" is the cause of symptoms. My cases, as shown in Table 3, were found to have chronic inflammation of the cystic duct remnant,

TABLE 3.—*Remnant Duct Surgery*

Patient	Age	Preop. X-Ray Visualization	Oper. Cholangiogram	Choledochotomy	Postop. Cholangiogram	Oper. Date	Remnant Duct Pathology
1	47	Yes	None	Yes	Yes	Jan. 1951	5.5 cm. Chr. inflam.
2	65	None	None	Yes	Yes	March 1951	3 cm. Chr. inflam.
4	58	None	None	Yes	Yes	Oct. 1951	2 cm. Chr. inflam.
3	66	None	None	None	None	May 1952	3.5 cm. Chr. inflam.
8	48	None	None	Yes	Yes	March 1955	2 cm. Chr. inflam.
5	44	1 Yes, 1 No	Yes	Yes	Yes	Feb. 1957	3 cm. Chr. inflam.
6	30	Yes	Yes	None	None	March 1957	6 cm. Chr. inflam.
7	63	None	None	None	None	May 1957	5.5 cm. Chr. inflam.
9	52	None	None	None	None	Aug. 1957	2 cm. Chr. cellulitis
10	66	None	Yes	None	None	Nov. 1957	7 cm. Chr. inflam.
11	54	Yes	Yes	None	None	Nov. 1957	2.5 cm. Chr. inflam.
12	58	None	Yes	None	None	Jan. 1958	7.5 cm. Chr. inflam. (single stone)
13	69	None	None	Yes	Yes	June 1958	7.5 cm. Chr. inflam. (stones in both ducts)
14	41	None	None	None	None	July 1958	3 cm. Chr. inflam. (no stones)

and at operation extensive scar tissue involving the common duct and remnant duct was found in each patient. Mechanically the scar tissue may disrupt the biliary tract functions by constricting, splinting, and producing traction of the common duct. These forces prevent compensatory dilation and constriction in relation to intraductal pressures within the choledochus. Larger remnant ducts may be anchored to the liver bed, further increasing the traction force. These mechanical factors plus chronic inflammation of the remnant ducts adequately explain the symptomatology. The presence of calculi in either or both ducts will intensify the symptoms, even to the point of producing typical biliary colic or hydrops of the cystic duct remnant when occlusion occurs.

Jaundice Enigma

The composite picture of symptoms described by the various writers on this subject is the same as mine except for the frequency of jaundice. The series of Beye,[2] Peterson,[3,4] Morton,[5] Garlock and Hurwitt,[10] and Glenn and Johnson [7] demonstrated a high incidence of jaundice, while the cases presented by me had no jaundice. The cause of jaundice in the reported cases is uncertain unless common duct stones were demonstrated. The suggestion that cholangitis and hepatitis may be responsible is not to be discarded. Out of the 200 cases reported before this series, 68 had stones in either or both cystic and common ducts.

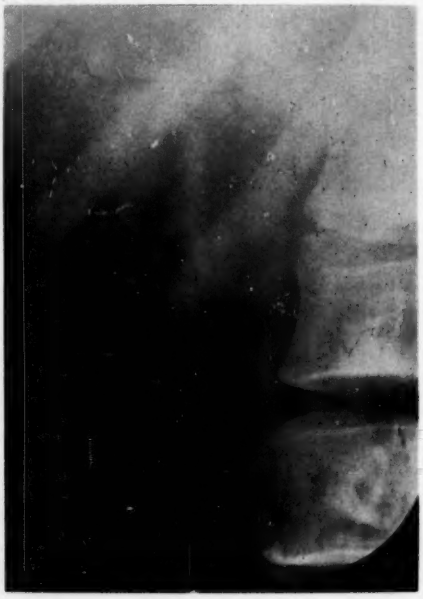
Private Practice Series of Remnant Cystic Duct

Each patient of this series of 14 cases was operated upon initially for gallbladder disease by an untrained or self-taught surgeon, as shown in Table 2. Twelve of these patients had continued or recurrent symptoms from one month to 30 years before they were diagnosed and operated on for "re-formed gallbladder." One patient developed symptoms 23 years after the original gallbladder surgery. Another patient was symptom-free for three years after cholecystectomy and then had a recurrence. The only patient giving a questionable history of jaundice was operated upon by an osteopathic physician.

Remnant Duct Surgery

The pertinent points of the 14 cases of remnant duct surgery here presented are shown in Table 3. The age range and sex distribution are not dissimilar to those reported by others. Roentgen examination demonstrated the "re-formed gallbladder" preoperatively in three patients, and one was questionable on two testings. Figure 1 is an x-ray reproduction showing the remnant cystic duct of Patient 6. Of those demonstrated, one was by oral dye technique and the two others by intravenous procedures. At a university hospital the questionable case was considered as possibly having a "re-formed gallbladder," but this case had no ductal visualization at the local hospital radiological department. A choledochotomy

Fig. 1.—Photograph of x-ray film of Patient 6, age 30, operated on, March, 1957. Arrow directs attention to the shadow interpreted as the remnant cystic duct.



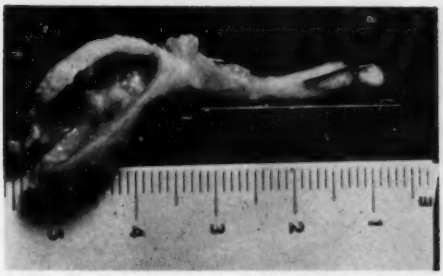


Fig. 2.—Photograph of the remnant cystic duct removed from Patient 12. Note calculus in distal end of lumen. This specimen measured in situ was 7.5 cm.

was performed on six of the patients, followed by postoperative cholangiogram in all. The operative cholangiogram was used on five of the last patients in order to avoid opening the common duct. Operative cholangiograms, since becoming available, were performed through the freed cystic duct, to avoid the trauma of choledochotomy. A single stone was found in the remnant cystic duct of one patient and multiple stones in both ducts of another. Figure 2 is a photograph of the cystic duct remnant removed from Patient 12. One patient[19] having a choledochotomy with exploration, irrigation, and dilatation, died 14 days postoperatively of acute hemorrhagic pancreatitis. This was the only mortality of the series, and the other patients have been symptom-free since their "re-formed gallbladder" operations.

Since this type of surgery is expected to yield good results, a long-time follow-up is not necessary to assess the cure rate in this type of surgical lesion, for it is established when the patient has completely recovered from the operation.

Contrary to techniques of sharp dissection, as described by other authors on this subject, the dissections carried out on the biliary ducts of these patients were done by the blunt procedure with a Mixter clamp to tease away scar tissue in order to avoid injury to other vital structures at the operative site. Tedious, slow, and difficult dissection was required to expose all of these remnant ducts.

Pathologic Findings

The pathologic finding in all resected ducts was chronic inflammation without evidence of neoplastic changes. A single calculus was found in one. Figure 2 shows this calculus. Multiple stones were present in the cystic and common ducts of another. The remnant ducts varied from 2 to 7.5 cm. in length, with equally proportionate range in the ductal diameters. Some ducts showed a bulbous tip. Figure 2 shows a specimen with a bulbous tip. The gross appearance of the duct in situ showed it to be tightly bound to the common duct by dense constricting tough scar tissue. Microscopic sections all show round cell infiltrations in the duct walls and about the intramural glands in varying amounts. Tidrick[20] suggests that the adenomatous hyperplasia of these vestigial intramural glands in association with chronic inflammation may be of etiologic significance. Figure 3 shows rather intense chronic inflammation about the glands in the wall of the duct of Patient 9. Figure 4 shows a photomicrograph, × 700, of cut section of the duct of Patient 3. Infiltration of round cells is less intense in this duct.

Clues for Diagnosis of Remnant Cystic Duct

Perhaps the most important factor in the diagnosis of a remnant cystic duct is that the surgical diagnostician be aware of the existence of such a condition. Encompassed in the enthusiasm of preparing this paper have been some discussions with other practicing physicians, not necessarily surgeons. It was rather amazing to learn that few of these doctors were aware of this complication of gallbladder surgery. Those who had heard of this problem knew little about managing the condition.

Case reports have not been presented, but some general observations about this group of cases will be given. Each of these patients had been previously treated by two or more physicians. They had been treated for many different diseases, such as perni-

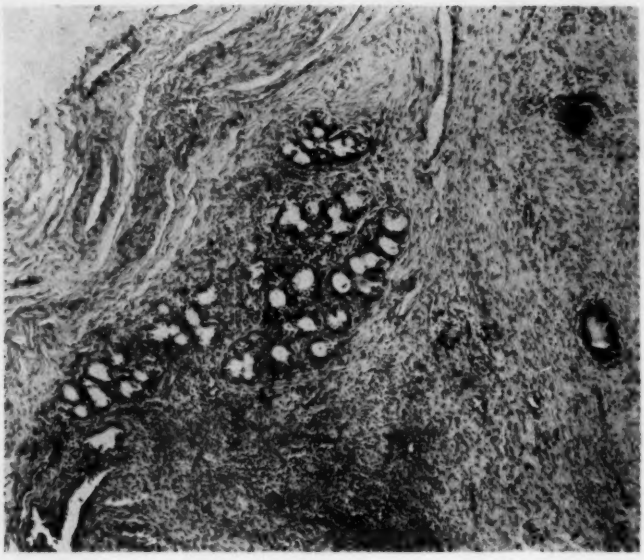


Fig. 3 (Patient 9).—Remnant cystic duct. Ductal epithelial lining is on the right, and scarred wall shows infiltrations of small round cells. They are concentrated about the glands in the wall. Microscopic section 57-1200. Photomicrograph reduced about ¼ from mag. × 300.

cious anemia, cardiac disease, intestinal obstruction, acute indigestion, pelvic diseases, and abdominal adhesions. Every patient had had one or more operations prior to primary cholecystectomy. Of the 14 patients 4 had been operated upon for intestinal obstruction after the *gallbladder* operation. The last two patients, particularly, had scars of their primary biliary operations so located that it did not seem logical that a total cholecystectomy could have been performed. Reoperation for "re-formed gallbladder" proved this deduction to be correct. Table 4 shows additional surgical data on Patient 5 (age 44), who had her remnant duct surgery in February, 1957. She had had an

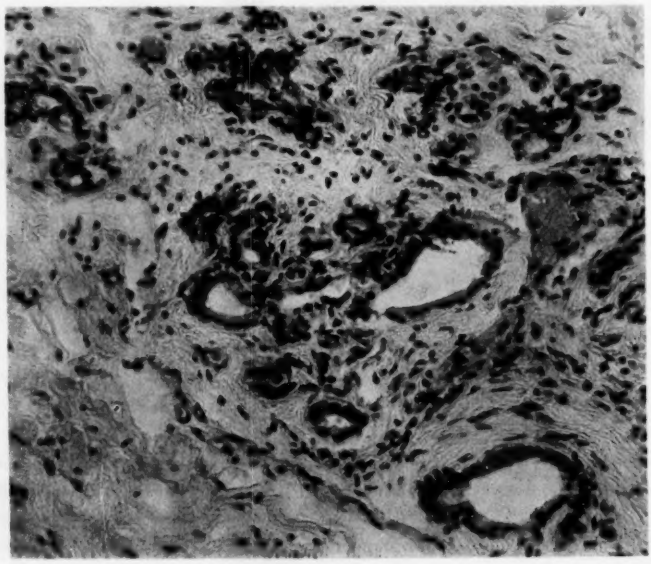


Fig. 4 (Patient 3).—Remnant cystic duct section of wall showing the glands surrounded by small round cells. Microscopic section 52-429. Photomicrograph reduced about ¼ from mag. × 700.

TABLE 4.—*Additional Surgical Data on Patient 5. Remnant Duct Surgery, February, 1957*

1933	Appendectomy and oophorectomy by general practitioner
1937	Oophorectomy and bilateral salpingectomy by general practitioner
1945	Cholecystectomy by general practitioner
1948	Laparotomy for intestinal obstruction by general practitioner
1950	Laparotomy for intestinal obstruction by general practitioner
1953	Subtotal hysterectomy by osteopathic physician
1954	Subtotal gastrectomy by osteopathic physician
1956	Cervical polypectomy by osteopathic physician
1956	Hemorrhoidectomy by general surgeon
1957	Excision of remnant cystic duct

From 1945 (cholecystectomy) until cystic duct operation, patient lost weight from 162 to 108 lb., owing to epigastric pain, nausea, and vomiting.

Consultation by internal medicine staff of a university college of medicine considered all symptoms of psychogenic origin.

May 1, 1958, patient was free of all G. I. symptoms and had gained weight from 108 to 142 lb.

appendectomy and oophorectomy followed by further pelvic surgery prior to her cholecystectomy in 1945 as shown in Table 4. All of these procedures were performed by a general practitioner practicing major surgery. In 1948 and 1950 this same practitioner performed laparotomies for intestinal obstruction. This patient then sought the help of an osteopathic physician, who performed a subtotal hysterectomy. The symptoms of "re-formed gallbladder" continued, and in 1954 the osteopathic physician performed a subtotal gastric resection for "peptic ulcer." The complaints still continued but they were severely clouded by symptoms suggestive of the dumping syndrome. This patient now had seven map-producing scars on her abdomen, and the cause of her symptoms was unresolved. She had been seen by many doctors and was even referred to the staff members of the department of internal medicine at a university hospital. She had been told by all that she was "neurotic" or had a "severe tension state." Although the follow-up period has been short, after remnant duct surgery, this patient has gained weight from 108 to 142 lb. She has no gastrointestinal symptoms, and is considered to be a stellar surgical success. It is rather interesting to note that in spite of two operations for intestinal obstruction, she had no general abdominal adhesions at the time of excisional therapy for the "re-formed gallbladder."

A most important point, since it was given by each of the 14 patients as part of the case history, is the fact that each patient had been told by the previous doctors that he was "nervous" or "neurotic."

Complete roentgen studies of the gastrointestinal tract were performed on each patient to attempt to exclude symptom-producing lesions before subjecting any of them to exploration for remnant cystic duct.

The decision to perform an operation for a remnant cystic duct was deduced in each patient by several factors, viz., (1) a history of having had cholecystectomy with continued or recurrent symptoms of indigestion; (2) completely negative roentgenographic studies of the gastrointestinal tract, reasonably ruling out other lesions which could produce symptoms; (3) the primary cholecystectomy having been performed before or about the time the "re-formed gallbladder" was reported as a cause of post-cholecystectomy symptoms; (4) the status of the original cholecystectomy surgeon (as indicated in Table 2), since most technical surgeons involved in these 14 cases were not trained surgeons, and may have been unaware of the remnant cystic duct as a residual complication of subtotal cholecystectomy, and (5) the location of the primary cholecystectomy scar and the consideration as to whether a total cholecystectomy could have been performed through the original incision.

Summary and Conclusions

Pertinent points from the reports of others on the subject of "re-formed gallbladder," or remnant cystic duct, are included in the historical data.

Remnant cystic ducts result from subtotal cholecystectomies and are productive of symptoms.

Photomicrographs of remnant cystic duct segments show chronic inflammation as a persistent characteristic.

Surgical "know how" is important and necessary to prevent this complication of cholecystectomy. This involves complete dissection of the cystic duct and ligating it accurately at its junction with the common duct.

The history and physical examination are the most important diagnostic features of this postcholecystectomy condition. After exclusion of other causes for gallbladder disease symptoms, the courage of the surgeon to recommend a surgical procedure is important.

Five factors which aid the surgeon to make the decision to operate for a remnant cystic duct are enumerated.

Excisional therapy is productive of a high cure rate for the symptoms of the remnant cystic duct.

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The Pathologic Significance of the Serum Amylase Concentration

An Evaluation with Special Reference to Pancreatitis and Biliary Lithiasis

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Since the introduction of the serum amylase test by Somogyi [1] and others, the discovery of an elevated serum amylase has usually been interpreted as conclusive evidence of the existence of severe inflammatory disease of the pancreas. The diagnosis of acute pancreatitis is now based much more frequently on examination of the blood serum than upon the actual examination of the pancreas; while before the introduction of the amylase test, the diagnosis of pancreatitis was made solely upon the actual discovery of the abnormality during celiotomy or autopsy.

Since the amylase test has seemed to offer a sure way of making the diagnosis of pancreatitis without operation, the so-called conservative treatment has become standard practice. Actually the presence of acute pancreatitis and its possible severity must remain in doubt as long as the diagnosis is substantiated only by an elevation of the serum amylase despite the presence of what seem to be appropriate physical signs.

Although elevations of the serum amylase have been noted to occur during illnesses other than acute pancreatitis,[2] such as perforated peptic ulcer, acute cholecystitis, intestinal obstruction, and intestinal strangulation, it is the general belief that this fact does not reduce the value of the serum amylase level as the basic diagnostic test for pancreatitis, because it has been said that the amylase elevations seen with these diseases are not as great as those observed with acute pancreatitis, and tend to occur later in the illness.[3]

Because of a number of disturbing experiences, which indicate that this belief is erroneous, suspicion was aroused that the diagnostic significance of the serum amylase determination is not what it has been purported to be. The following case summaries illustrate two of these experiences.

CASE 1.—A man 40 years old suffered upper abdominal pain, vomiting, and fever 48 hours after a subtotal gastrectomy for obstructing posterior duodenal ulcer. The serum amylase concentration was 3,198 Somogyi units/100 ml. Acute postoperative pancreatitis was thought to be the cause of his trouble, and because of the consultant's belief that surgical intervention is not to be practiced during the acute phase of pancreatitis, only supportive measures were employed. Uncontrolled peripheral circulatory failure and jaundice soon followed, and he died 48 hours after the pain began. Upon autopsy his pancreas was found to be only slightly edematous, while the entire jejunum and upper ileum had passed behind the gastroenterostomy, twisted its mesentery, and died. Had a serum amylase not been determined, per force, a surgical correction of the internal hernia would have been undertaken, because all the signs pointing to an intra-abdominal catastrophe existed. Were it not for the very high amylase and the interpretation placed upon this determination, the outcome might have been infinitely better.

CASE 2.—A woman 71 years old was admitted to Barnes Hospital after a four-hour illness characterized by upper abdominal pain, nausea, and vomiting. A 3,800 serum amylase was found and the physical examination indicated that a ballotable mass existed in the right upper quadrant of her abdomen. A diagnosis of acute pancreatitis was

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made, and a nonoperative course was elected. She continued quite ill, and on the fourth day of the illness she became jaundiced. Interim x-ray examinations of her abdomen showed some dilated loops of small intestine in the upper abdomen. Because she failed to improve, a celiotomy was performed. The gallbladder was distended, inflammed, and contained many small stones. The common bile duct was greatly dilated. The pancreas and stomach, duodenum, and mesentery of the transverse colon were normal. A small gallstone impacted within the ampulla of Vater was dislodged, and thereupon a 2 mm. Bakes dilator passed easily into the duodenum. A T-tube was left in the common bile duct, and the gallbladder was removed. She recovered quickly.

A preliminary investigation was accomplished in 1955. A consecutive series of 10 persons who had attacks of upper abdominal pain coupled with elevations of the serum amylase above 1,000 Somogyi units/100 ml. (normal 80-150) were operated upon within six weeks after onset of their illness.

Evidence of pancreatitis was found in only one of them and in this case acute cholecystitis and cholelithiasis were discovered also. Peculiarly in the other nine cases, at the time exploration was performed, there were no visible or palpable signs of the existence or preexistence of pancreatitis; that is, there was no fat necrosis or significant enlargement or induration of the pancreas. Although it was recognized that inflammation or edema of the pancreas might well have disappeared before the operative examination was done, it was considered unlikely that evidence of the existence of a suppurative, necrotizing, or hemorrhagic pancreatitis would have disappeared. In seven of these nine cases stones were found in the gallbladder, the common bile duct, or both. In one, a patient who had previously been operated upon and found to have stones in both the common bile duct and the gallbladder, a greatly dilated common bile duct and a duodenal diverticulum were discovered. These structures emptied into the duodenum through a common opening. In the remaining patient, the biliary tree was normal, but a carcinoma of the body of the pancreas existed. This person had been discharged from the hospital only two months previously after recovery from an illness which was diagnosed as acute pancreatitis because a serum amylase concentration in excess of 1,000 Somogyi units per 100 ml. had been found.

These experiences indicated to us (1) that an elevation of the serum amylase does not delineate the severity of pancreatic disease, and (2) that the serum amylase may be greatly elevated by such things as strangulatory obstructions of the intestine and acute cholecystitis and choledocholithasis without there being any signs of pancreatic disease whatsoever.

A study was undertaken of the 1949-1954 records of the Barnes and St. Louis City Hospitals on which a final diagnosis of acute pancreatitis was recorded by virtue of (1) a serum amylase of over 500 Somogyi units coupled with a compatible history and physical signs, and/or (2) the discovery of signs of pancreatitis during an operation, or an autopsy. Cases showing only postoperative elevations of serum amylase were not included in this study. One hundred thirty-eight records falling into one or more of these catagories were discovered. In 48 of these the organic abnormality existing within the abdomen is still in doubt, because neither an operation nor an autopsy was performed.

In the total five-year sample the amylase was 1,000 Somogyi units or higher in 103 cases; between 500 and 1,000 in 21; and less than 500 in 11 cases. In three cases of proved pancreatitis the amylase test was not recorded. A celiotomy permitting the examination of the pancreas and the biliary ducts or an autopsy had been performed at varying intervals of time (0-8 weeks) after the beginning of the illness in 67 and 26 cases, respectively. Because an autopsy was performed upon three patients upon whom a preceding exploratory laparotomy had been done, the actual working sample for the study consists of 90 cases instead of 93.

During the last 15 years the authors of papers dealing with pancreatitis have generally assumed that pancreatitis existed

TABLE 1.—*Operative Findings, (1949-1954) in Sixty-Seven Cases with Recorded Diagnosis "Acute Pancreatitis"*

Operative Findings	Highest Serum Amylase Somogyi Units/100 Ml. 1,000 or Greater	500-1,000	Less Than 500	Died
Biliary lithiasis No pancreatitis	43	7	0	1
Pancreatitis Associated biliary lithiasis	5	0	5	2
Pancreatitis No biliary tract disease	1	1	2	0
No pancreatitis No biliary tract disease	1	2	0	2
Totals	50 (75%)	10 (15%)	7 (10%)	5(7%)

whenever elevations of the serum amylase were found. We have adopted a completely opposite view and have considered that the formulation of a diagnosis of pancreatitis is justified only upon the discovery of signs of the disease such as fat necrosis, or remarkable enlargement or induration of the pancreas by a surgeon or a pathologist. The correlations of these signs of pancreatitis with the serum amylase concentrations are recorded in Table 1 (operative) and Table 2 (autopsy). Three patients exhibiting serum amylase above 500 Somogyi units preoperatively died after being operated upon (5%). Two other deaths occurred postoperatively. These two persons actually had suppurative pancreatitis, although the disease was not suspected preoperatively in either case.

TABLE 2.—*Autopsy Findings, (1949-1954) in Twenty-Six Cases with Recorded Primary Diagnosis "Acute Pancreatitis"*

Autopsy Findings	Highest Serum Amylase Somogyi Units/100 Ml. 1,000 or Greater	500 to 1,000	Less Than 500	No Amylase Test Done
Biliary lithiasis No pancreatitis	2	1	0	0
Pancreatitis Associated biliary lithiasis	9	0	4	2
Pancreatitis No biliary tract disease	3	0	4	1
Totals	14 (54%)	1 (4%)	8 (31%)	3 (11%)

The most frequent lesion to be found between 1949 and 1954 in the Barnes and St. Louis City Hospitals with or after elevations of the serum amylase above 500 Somogyi units per 100 ml. of serum was biliary lithiasis, and the least frequent was primary acute pancreatitis. In the autopsy series there were two cases with serum amylase elevations above 1,000 Somogyi units and one with a serum amylase above 500 but less than 1,000 units in which exhaustive gross and microscopic examinations of the entire pancreas uncovered no evidence of inflammatory disease of this organ. In addition, eight persons (30% of the autopsy series) were found to have pancreatitis during necropsy, although their serum amylase concentrations were normal when the analysis was performed. Although the serum amylase values of these eight cases may have been above normal at some time during the illness, their physicians, while very alert to the diagnosis of pancreatitis and enthusiastic about the amylase test, were not successful in procuring a sample of blood containing more than the normal amount of amylase even though the disease existed. In addition, in three cases found to have pancreatitis at necropsy, the amylase tests were not performed because the physicians did not suspect the existence of pancreatitis.

A review of the current practice at the Barnes Hospital (1955-1957) indicated that there were 44 patients whose illness was diagnosed as acute pancreatitis by the criteria used in selecting the 1949-1954 series. Table 3 illustrates the findings in 22 patients who were operated upon. There were no deaths in the other 22 patients.

Comment

In the combined series, 1949-1954, operative confirmation of the diagnosis of acute pancreatitis in association with serum amylase elevations above 500 Somogyi units/100 ml. were observed in 7 in 60

TABLE 3.—*Operative Findings (1955-1957) in Twenty-Two Cases with Recorded Diagnosis "Acute Pancreatitis"*

Operative Findings	Highest Serum Amylase Somogyi Units/100 Ml.				
	1,000 or Greater	500-1,000	Less Than 500	No S. A. Done	Died
Biliary lithiasis No pancreatitis	6	0	0	0	0
Pancreatitis Associated biliary lithiasis	8	0	1	1	1
Pancreatitis No biliary tract disease	2	0	2	2	1
Totals	16 (73%)	0 (0%)	3 (13.5%)	3 (13.5%)	2 (9%)

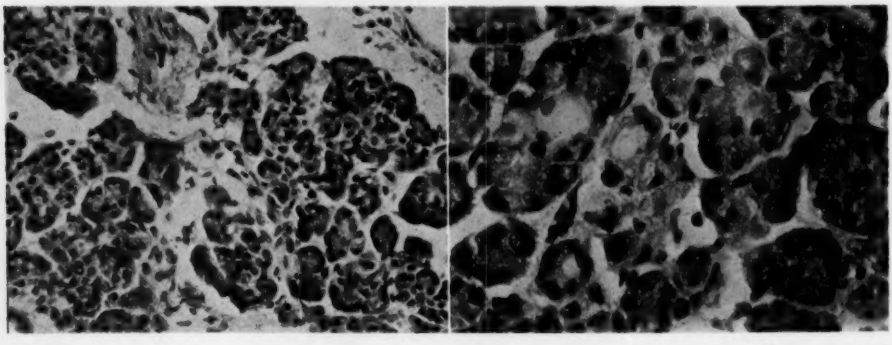
cases, a correlation of 0.12. In the 1949-1954 autopsy series this correlation was 12 in 15 autopsies, or 0.80. During this same period of time biliary lithiasis was associated with elevation of the serum amylase above 500 Somogyi units/100 ml. in 55 of 60 patients in the operative series (a correlation of 0.91) and in 12 of 15 in the autopsy series (a correlation of 0.80). Biliary lithiasis was observed in 60 of 67 patients in the total operative series and in 16 of 26 in the complete autopsy series or correlations of 0.90 and 0.62 respectively.

The correlation of elevations of the serum amylase above 500 Somogyi units/100 ml. with pancreatitis demonstrable at operation rose to 10 in 16, or 0.62 in the 1955-1957 series. In this series biliary lithiasis was correlated with amylase elevations in 14 of 16, or 0.9. In the entire 1955-1957 series biliary lithiasis was observed in 16 of 22, or 0.73.

This recent experience and the autopsy series alone provide evidence that acute elevations of serum amylase concentration above 500 Somogyi units per 100 ml. occur as frequently with biliary lithiasis without pancreatitis as they do with pancreatitis without biliary lithiasis. Absolute proof that elevated serum amylase levels may be noted in the complete absence of pancreatitis may only be obtained from microscopic examination of the pancreas during or after the attack has occurred. An approach to such proof is afforded by three cases in the autopsy series and by the following example.

A woman 44 years old had severe epigastric pain for 24 hours. This pain radiated through to the tip of the right scapula and retrosternally. She had epigastric tenderness and abdominal muscle spasm. The white blood count was 9,200. Her trouble was thought to be acute pancreatitis because her serum amylase value was 915 Somogyi units %. She improved rapidly for a time, although the serum amylase levels remained about 300 So-

Fig. 2.—Photomicrographs of a needle biopsy specimen taken from the midportion of the pancreas of a patient thought to have acute pancreatitis because of elevation of the serum amylase concentration to 4,000 Somogyi units/100 ml. four days before operation. Reduced about 35% from mag. × 100 (left) and × 300 (right).



mogyi units %. Cholecystography demonstrated multiple small gallstones with faint visualization of the gallbladder. The severe abdominal pain returned 11 days after the first pain was felt, and her serum amylase promptly rose to 4,000 Somogyi units %. The alkaline phosphatase level was 10.5 Bodansky units. A laparotomy was performed four days later when the serum amylase was 400 Somogyi units %.

Her entire biliary tree was found to be greatly dilated. Her gallbladder was partially filled with stones averaging about 3 mm. in diameter. The ampulla of Vater permitted the easy passage of a No. 6 Bakes dilator. The common bile duct contained thick yellow sludge. The pancreas was normal in size, consistency, and color. Her gallbladder and appendix were removed, and a Silverman needle biopsy was performed in the superior portion of the middle one-third of the pancreas (Fig. 2). This biopsy showed only normal pancreas. The postoperative course was uneventful. A postoperative cholangiogram was normal, and the pancreatic duct was not visualized.

This case raises an obvious question: What pathways exist, other than abnormalities of the pancreatic parenchyma, for the entry of large quantities of pancreatic amylase into the circulation? The possibility that amylase might gain access to the circulation by way of the biliary ducts and the hepatic parenchyma was tested by injecting canine pancreatic juice into the obstructed common bile ducts of anesthetized dogs at rates that did not raise the pressure in the common duct above that against which pancreatic juice can be secreted.

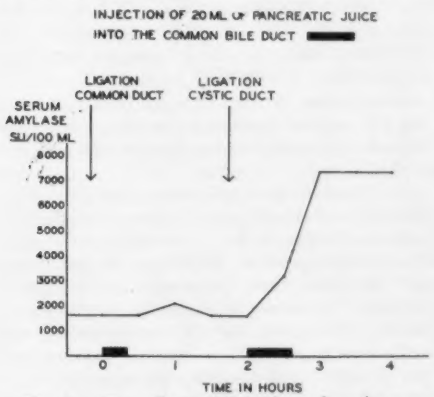


Fig. 1.—The effect of injection of canine pancreatic juice into the common bile duct on the serum amylase concentration. The initial injection was made at a pressure of 20 cm. of water. The second injection was made at a pressure of 30 cm. of water.

Figure 1 depicts one such experiment. The injection of 20 ml. of canine pancreatic juice into the distally obstructed common duct of a dog while the cystic duct was open effected no change in the concentration of amylase in the blood of the recipient. However, upon ligation of the cystic duct the injection of 20 ml. of pancreatic juice into the distally obstructed common duct quickly effected a fivefold increase in the concentration of amylase in the serum. *Pancreatic amylase is capable of entering the circulation through the biliary ducts and the liver.**

This route may be the means whereby large quantities of amylase gain entrance to the circulation during cholecystitis and obstructions of the common duct without there being any concomitant affliction of the pancreas.

Conclusions

The correlations of the serum amylase test in the three series of cases permit the following conclusions:

1. The serum amylase test alone cannot be used to differentiate between obstructive biliary lithiasis without pancreatitis, pancreatitis without biliary lithiasis, and concomitant pancreatitis and biliary lithiasis.

2. Accurate assessment of the merits of "conservative" or "nonoperative" regimens of treatment of acute pancreatitis is impossible; the diagnosis of pancreatitis cannot be made with certainty without an autopsy or celiotomy.

3. The mortality of acute pancreatitis is really unknown in any series of cases in which a high serum amylase, rather than internal visible evidence of the disease, is accepted as sufficient grounds for making a diagnosis.

A very good correlation in each series was observed between elevation of serum amylase and the presence of biliary lithiasis.

The over-all operative mortality when limited to those patients who demonstrated

* An experimental elucidation of this phenomenon is now being attempted by Dr. Bernard.

elevation of the serum amylase was 4 of 76, or 5%. The operative mortality in the group proved to have pancreatitis was 4 in 31, or 13%. These mortality statistics do not support the rather commonly held view that great hazard attends operations upon patients who have had pancreatitis.

The data do not suggest any method for improvement in the treatment of acute pancreatitis in any of its forms.

Summary

The diagnosis and the mortality rate of acute pancreatitis cannot be ascertained in any series without examination of the pancreas at first hand.

A mortality of 5% was observed in those patients operated upon after prior elevation of the serum amylase. This mortality was 13% in those patients proved to have pancreatitis at operation.

Elevations of the serum amylase above 500 Somogyi units/100 ml. may occur in the complete absence of demonstrable pancreatic disease.

Better methods for the preoperative diagnosis of pancreatitis should be sought.

600 S. Kingshighway.

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DISCUSSION

ON PAPERS BY DRS. EISEMAN, W. H. BROWN, VIRABUTR, AND GOTTESFELD; BY DR. MERLE J. BROWN, AND BY DRS. BERNARD, CRISCIONE, AND MOYER.

DR. JOHN H. GRINDLAY, Rochester, Minn.: Dr. Eiseman asked me to make some remarks concerning the first of this group of three papers, given by Dr. W. H. Brown. First I would like to make a remark amounting to a confession pertaining to the paper given by Dr. Merle Brown.

Once while I was chief of surgery at Maguire Hospital in Richmond, during the War, I was persuaded by my medical colleagues to remove the gallbladder of a soldier patient with an early acute cholecystitis. I say it was foolish because in that patient I saw what I had never seen before—the most edematous gallbladder in my experience, even during my training days. I removed it in a retrograde fashion, and when I got to the cystic duct it was as though it had priapism.

Just as Ulysses steered his course in the Straits of Messina, I ligated the duct at the point which I felt avoided any danger of ligation of an hepatic artery, or damage to a duct. I am certain that this patient is one of this group, or is in someone's group of a remnant of a common duct series.

Concerning Dr. Eiseman's paper, given by Dr. W. H. Brown, I am not surprised at the results. I am certain the data are correct. I would like only to point out that the dog has no common channel of pancreatic and biliary drainage. It also has no real ampulla of Vater. The sphincter of the common duct is rather rudimentary, with only delicate muscular layers in the muscularis mucosa at the lower end of the bile duct.

I would remind you that the main sphincteric action is provided by the duodenal musculature, because the common duct in the dog has a transverse diagonal course through the duodenal musculature. How much one can apply the results obtained in dogs to man, who has an entirely different set-up, I don't know.

DR. C. ALAN MCAFEE, St. Louis: I would like to discuss Dr. Bernard's paper.

I thought for a number of years that the common cold, thrombophlebitis, and pancreatitis were the most overtreated diseases known to man. Now Dr. Bernard tells us that not only are we overtreating this disease, but we are overdiagnosing it to the tune of almost one and a half false positive cases to every one case of true pancreatitis. At least this is true when the amylase has been used as the primary or sole index for diagnosis.

Furthermore, he certainly has emphasized the fact that amylase levels may rise over 1,000 in the face of intraperitoneal catastrophes such as gangrenous bowel

It is possible that his figures might vary somewhat from those of others. We have a rather happy population in St. Louis, particularly since Bill Veeck transferred the Browns to Baltimore, and therefore there are very few alcoholics. [Laughter] I am also intrigued by Dr. Bernard's possible explanation for the evaluation of the serum amylase in the face of cystic duct obstruction. Certainly this deserves further work.

I would also like to hear someone come up with a combination of findings via the laboratory, such as intravenous cholecystograms, lipase levels, and so on, that might give us a little more accurate means of arriving at a diagnosis of pancreatitis.

As we stand at the present time, the most important factors in the management of the patient with an elevated amylase are careful history, physical examination, and the response of the patient to our supportive care during his period of observation.

This means of, course, that I do not approve of exploratory laparotomy on all patients with abdominal pain and elevated amylase levels. Possibly Dr. Bernard will approve the laparotomy approach.

Another problem is how far we shall go in an exploratory laparotomy in a patient found to have gross evidence of pancreatitis. Shall we actually dare to explore that common duct with Bakes dilators?

DR. EDWARD O. FERRIS, Rochester, Minn.: I appreciate very much the opportunity to discuss Dr. Brown's paper. First, I want to congratulate him on the diagnostic acumen evident from his discovery of 14 such cases in his own private surgical practice.

I agree with Dr. Brown's statement that removal of the diseased stump of a cystic duct is successful in relieving symptoms in a high percentage of cases. At the clinic I represent we have found that if adequate indications for cholecystectomy were present originally, 70% of the patients with continuing symptoms obtain relief by the second operation, in which the cystic duct, with or without stones, is removed.

In surgery of the biliary tract the motto should be "gently and accurately"; and, of course, in Dr. Brown's cases the original cholecystectomy had been performed inaccurately by others.

Dr. Brown has made a plea for complete removal of the cystic duct at the time of cholecystectomy, but let me add a word of warning. The usual cystic duct is not more than 6 or 7 cm. in length and joins the common hepatic duct at a slight angle. This slightly angular type of union occurs in 75% of cases. However, in 17% the cystic duct parallels the common hepatic duct for some distance before joining it to form the common duct. In the remaining 8% the cystic duct spirals the common hepatic duct before joining it. Regardless of whether the union is of angular, parallel, or spiral type, the 5 cm. nearest the gallbladder contains the spiral valves of Heister, through which instrumental exploration is impossible, and in which stones usually become impacted and obstruction and infection occur. Most of the pathologic developments in remnants of the cystic duct occur in this short segment, which might be described as the readily apparent cystic duct. Beyond this point, the parallel and spiral types become intimately attached to the hepatic duct. For most of us it is unwise to attempt complete removal of these types—first, because of the danger of damage to the common hepatic duct with ensuing stenosis; and, second, because this distal portion may be explored instrumentally and roentgenologically.

My last point has to do with obstructive jaundice. Several authors have mentioned and even stressed the occurrence of jaundice as a factor associated with disease of the remnant of a cystic duct. Dr. Brown did not. Obstructive jaundice implicates the common duct; and no matter whether the surgeon is removing the remnant of a cystic duct or the whole cystic duct and gallbladder, he still must demonstrate that the common duct is free of obstruction.

DR. EVERETT LEE STROHL, Chicago: I should like to confine my remarks to the paper by Dr. Merle J. Brown.

First of all, I should like to commend Brown for reemphasizing the pathology of the cystic duct remnant. I was shocked to hear him say that the incidence of pathology in this area runs between 10% and 15%.

Secondly, I should like to ask a question. In the patient who died with acute hemorrhagic pancreatitis, was a long-armed T-tube used?

We have emphasized the dangers of using a long-armed T-tube, and have reported seven patients who died after the use of a long-armed T-tube with acute hemorrhagic and necrotizing pancreatitis.

Lastly, I would like to reiterate something that one of our past presidents, Dr. Robert Zollinger, has pointed out. In Dr. Brown's last patient, who had innumerable surgical procedures, the outstanding symptom was epigastric pain, nausea, and vomiting. If you will recall, Dr. Zollinger demonstrated that an increase in pressure within the common bile duct or the cystic duct produces that syndrome of symptoms. I am sure that the diagnosis could have been made on a clinical basis many years earlier, had these clinical findings been cautiously analyzed. "Disease often tells its secrets in a casual parenthesis."—Harrison.

DR. ALFRED M. LARGE, Detroit: I should like to compliment Dr. Brown and Dr. Eiseman on their presentation, but I, too, should like to discuss Dr. Merle Brown's paper on the diseased cystic duct remnant.

I think most of us have been pleasantly impressed by the fact that the majority of these people are relieved of their symptoms when the cystic duct remnant is removed, even though no stone may be found. This has been true in our own small series in Detroit, and I would like to offer a hypothesis to explain this phenomenon, since at least to our way of thinking no reasonable one has been advanced up to this time.

Many of you know that we have been interested in a condition lately which we have referred to as regurgitation cholecystitis and cholelithiasis, a condition in which, when ever the sphincter of

Oddi is cut or the common duct anastomosed to the intestine, bypassing the sphincter, cholecystitis and perhaps cholelithiasis may develop if the gallbladder is left in.

Recently we have been interested to find evidence (which I shall not quote now) that at least in certain persons who have patulous sphincters, cholecystitis and cholelithiasis may develop even in the absence of a cut sphincter or in the absence of duct transplantation.

If one will accept this last item as being correct, then if certain patients have this factor at play after the gallbladder is present, this factor is still at play.

You see, the reason we think regurgitation cholecystitis develops is that the gallbladder then just acts as a pouch in the biliary tract, and any infection there will lie in the diverticulum. It is our feeling, then, that if a cystic duct remnant is present, a similar type of nidus may be present and may exist for the perpetuation of any ascending infection. If the gallbladder is gone, or if the cystic duct remnant is gone, then the continuous washing effect of bile passing into the intestine will prevent such regurgitation from occurring.

The only point again that I would like to emphasize in closing, in this respect, is that we, too, have found these cystic duct remnants to be chronically inflamed, just as Dr. Brown showed in his slides, which is some evidence in support of this idea. We have also found that the bile in the common duct in these patients has yielded positive cultures. So, although this is by no means established, we are accumulating evidence to show that this regurgitation phenomenon, an old, old idea, may be indeed a true one, and we think it may be of importance in the cystic duct remnant.

Dr. Robert T. Tidrick, Iowa City: There are occasions when it is possible to make sequential observations on these things.

[Slide] I am sorry that Dr. Frank Peterson isn't here to discuss this, because this is one of the early patients in the Peterson-Beye series. These two gallbladders that you see here are separated by an interval of 22 years, and the one on the right represents the gallbladder which the patient carefully put in a pickle jar and saved. Twenty-two years later, when Dr. Frank Peterson removed the elongated cystic duct stump which you see on the left, we had the visible evidence of the two of them.

It certainly is suggestive from Dr. Brown's series that the experience of the surgeon has a lot to do with whether there will be a recurrence of cystic duct difficulty or so-called "re-formed gallbladder," but it isn't always the case.

[Slide] Sometimes there are opportunities for surgeons to make a detailed observation of the condition of the cystic duct stump, and several years later, at reoperation, find that this condition has developed anyway. In such a case, shown here, this huge, elongated remnant was removed six years after exploration of the cystic duct stump and repair of common bile duct stricture. In its extended state this measured 11 cm.

Perhaps the interesting concept which Dr. Large has reopened will throw some light on this.

Dr. W. H. Brown, Denver: I would like to thank Dr. Grindlay for his discussion. Certainly we agree that there is a difference in the anatomical configuration of the sphincter in the dog and the human, in that in the human the circular fibers at the ampulla are more important. However, in our series of five cases which we measured for 8 to 10 weeks after sphincterotomy, there was a profound drop on yield pressure. Sometimes we could not even measure the postoperative pressure, but in varying lengths of time this always did return to above the presphincterotomy base-line pressure.

Dr. Merle J. Brown, Davenport, Iowa: Before someone asks me how many laparotomies we did to find 14 cases, may I say I have a 100% score up to now. I won't swear it will last too long.

I appreciate Dr. Ferris' comments very much, and to have him back up my thesis makes me feel good.

Dr. Strohl, I did not use a long-armed T-tube. As a matter of fact, I have never subscribed very much to its use, and so none was inserted here. The woman died from acute hemorrhagic pancreatitis, which was demonstrated at postmortem examination.

Dr. Large has a good thesis on regurgitation cholecystitis, and perhaps that has some bearing in the production of chronic inflammatory reaction that we find about the intramural glands and cystic duct walls. That seems to be in all sections that I have, and I have had them all photographed—mass concentrations of the inflammatory cells about the intramural glands rather than in the mucosal area of the duct.

Dr. Tidrick's slides certainly have helped to back up my thesis.

Dr. Harvey R. Bernard, St. Louis: I would like to thank Dr. McAffee for his discussion. I would like to emphasize that we do not believe we know how to treat pancreatitis. I have no data to support any operative procedure when acute pancreatitis is actually found at operation.

I believe the indications for operation, however, in patients like this are the following:

1. Obvious intra-abdominal catastrophe, following adequate preoperative preparation

2. Failure of improvement under careful observation

3. The presence of biliary stones with removal at the time considered optimal by the surgeon.

Immediate Results in the Treatment of the Perforated Peptic Ulcer, 1942-1957

CONSTANTE N. FIRME, M.D.; JOHN R. PAINE, M.D., and RICHARD W. EGAN, M.D., Buffalo

Introduction

In 1954, the *Statistical Bulletin of the Metropolitan Life Insurance Company* published a study of surgical mortality associated with the treatment of various lesions by major surgical operations.[1] In all instances cited, surgical mortality had apparently been reduced during the decade of the 40's by at least one-half and in several instances by more than four-fifths. For several reasons, however, there would seem to be cause for doubt as to whether this marked and well-recognized decrease in general surgical mortality were also true in the case of the acutely perforated peptic ulcer. To obtain more information on this point, we have critically studied all the patients treated for an acute perforation of a peptic ulcer at the Buffalo General Hospital for the 15-year period from Jan. 1, 1942, to Jan. 1, 1957. These cases have been divided for comparison into three groups, each covering a consecutive period of five years. Various factors in diagnosis and management have been studied to try to determine what, if any, improvement has occurred in recent years in the treatment of this condition.

A detailed analysis of the fatalities has been made in an effort to ascertain the controllable factors contributing to the hospital mortality rate.

General Observations

A total of 179 patients with perforated peptic ulcer have been treated or found at autopsy at the Buffalo General Hospital during the 15 years comprised in this study. In Table 1 the division of these cases among the three five-year periods chosen for comparison as well as the incidence according to sex is given.

TABLE 1.—*Incidence According to Years and Sex*

	Males	Females	Total
1942-1946	58	8 (12%)	66
1947-1951	43	5 (10.5%)	48
1952-1956	56	9 (14%)	65
	157	22 (12%)	179

The ratio between males and females is approximately that reported in other published series. There were 174 spontaneous perforations. In two instances patients were being treated with cortisone at the time of the perforation. In three patients the perforation followed immediately a major abdominal operation.

The relative incidence of gastric ulcer perforation has been slightly greater during the later years of this study than during the earlier years. Somewhat over one-half of the women in our series had perforations of gastric ulcers, while only 28% of the men had similar lesions. Eleven patients had had previous perforations. Two simultaneous perforations were found in one instance,

TABLE 2.—*Location of Perforation*

	Duodenal	Gastric	Marginal	Not Stated	Total
1942-1946	49	16	—	1	66
1947-1951	31	17	—	—	48
1952-1956	42	22	1	—	65
	122 (68%)	55 (31%)	1	1	179

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From the Department of Surgery of the Buffalo General Hospital and the University of Buffalo School of Medicine.

and three patients had multiple ulcerations in addition to the perforation. Only eight patients gave a history of previous upper gastrointestinal tract hemorrhage. In one instance, massive bleeding and perforation were concomitant.

Approximately three-fourths of our patients gave a history of symptoms referable to the gastrointestinal tract prior to the rupture of their ulcers. These symptoms varied from an indefinite fullness or discomfort after meals to the classical hunger pain relieved by food or alkalies. In 44 instances no history of any symptoms suggesting ulceration could be obtained. No clinical history was available for 11 patients.

The diagnosis was usually readily established on the basis of history and physical examination alone. Most patients when first seen were generally and acutely ill with marked muscle spasm of the abdominal wall and diffuse tenderness. Only 10%, however, were considered to be in a state of shock when first seen, and the temperature was only rarely recorded as over 100 F. The white count taken at the time of admission was neither diagnostic nor prognostic, although in the differential count a left shift was the rule.

Ninety-three patients were examined roentgenologically to detect the presence or absence of free gas in the peritoneal cavity. In 65 patients (70%) pneumoperitoneum was demonstrable.

Treatment

Management was basically the same in all the 159 cases that were operated upon. After the diagnosis was established, decompression by means of a nasogastric tube was immediately initiated. Intravenous fluids were simultaneously given to correct dehydration and electrolyte imbalance. Blood was transfused when indicated prior to operation. Operative treatment was simple closure of the perforation in all except one case, in which a subtotal gastric resection was performed primarily. In this instance a 39-year-old man was admitted to the hospital for an elective resection for a duodenal ulcer. At the time of operation a previously unsuspected small perforation with minimal soiling of the peritoneal cavity was found.

The method of closure of the perforation varied appreciably only during the first five-year period. Invagination by purse-string suture and one- to three-layer closure with interrupted silk or chromic absorable surgical sutures were interspersed with the omental patch technique of Graham.[2] Beginning in 1947, Graham's method was employed in 96 out of 100 instances.

Drains were placed in the peritoneal cavity in 34 of the 159 cases operated upon, approximately 21%. Antibiotic drugs were used liberally throughout the entire series. In 1942-1943, sulfanilamide powder 5-10 gm. was usually sprinkled in the peritoneal cavity before closure. In 1944-1945, sulfadiazine and sulfathiazole were used more or less routinely. Penicillin was administered for the first time in 1945, a total of 1,380,000 units being used to treat three patients. In 1946, all of the eight patients operated upon were given penicillin with an average dose per patient of 1,300,000 units. Streptomycin was first used in 1948. From that time on, each patient received about 4,000,000-6,000,000 units of penicillin and 6-8 gm. of streptomycin during the postoperative period. During the latter years, a variety of antibiotic drugs were employed, such as chloramphenicol (Chloromycetin), chlortetracycline, (Aureomycin), erythromycin and oxytetracycline (Terramycin).

During the entire period of the study, only 20 patients were not operated upon. Five were considered to be moribund. Three refused to be operated upon. Three were treated conservatively because it was thought that the perforation had closed spontaneously. In nine patients, the diagnosis of perforation was not suspected.

Complications

Complications encountered during the postoperative period were similar to those reported by other authors and occurred in

TABLE 3.—*Postoperative Complications*

	1942-1946	1947-1951	1952-1956	Total
Wound infections	5	1	4	10
Wound disruption	2	7	1	10
Atelectasis	0	2	1	3
Pneumonitis	1 *	3 *	1	5
Peritonitis	2 **	0	1 *	3
Subphrenic abscess	0	0	1	1
Obstructive jaundice	1	0	0	1
Septicemia	1 *	0	0	1
P. O. psychosis	1	0	0	1
Pulmonary embolus	0	1 *	0	1
Coronary thrombosis	0	1	0	1
Pyloric obstruction	0	1	0	1
Transfusion reaction	0	0	1	1
Thrombophlebitis	0	0	1	1
Hemorrhage from closed ulcer	0	0	1 *	1
Bronchial aspiration	0	0	1 *	1
	13	16	13	42

* Death due to complications.

25% of the patients. Forty patients had 42 complications, 9 of which were fatal.

Wound infections and disruptions comprised approximately one-half of all the complications. Pulmonary complications were next commonest, accounting for approximately 20% of the total.

Analysis of the Hospital Fatalities

Of 179 patients with acutely perforated gastroduodenal ulcers 34 (17.3%) died in the hospital. Of 159 patients operated upon, 17 (10.7%) died, and there were 14 deaths in the 20 cases not operated upon. There was no significant variation between each of the three five-year periods surveyed (Table 4).

TABLE 4.—*Mortality in Patients with Perforated Peptic Ulcer, (1942-1956)*

	Patients Operated Upon	Deaths	% Mortality
1942-1946	59	7	11.9
1947-1951	44	4	9.9
1952-1956	56	6	10.7
	159	17	10.7
	Patients Not Operated Upon	**Deaths**	**% Mortality**
1942-1946	7	6	85.7
1947-1951	4	4	100.0
1952-1956	9	4	44.4
	20	14	70.0

Factors Influencing Mortality

Several factors can be recognized as apparently influencing this disappointingly high hospital mortality rate from acutely perforated peptic ulcers.

Age of the Patient.—Although age may not be considered to be a prime factor influencing the mortality rate, 80% of the fatal cases in this series occurred in patients 50 years of age or older. There were 24 fatalities among the 86 patients who were 50 years of age or older. Conversely, there were 93 patients under the age of 50 years, and only 7 fatalities in this group. In the operative series of 159 patients there were 14 fatalities in the 71 patients over 50 years of age and 3 fatalities in the 88 patients under 50 years of age (Table 5).

Time Interval Between Perforation and Surgery.—The hospital mortality rate of the operative series increased significantly

TABLE 5.—*Mortality of Acutely Perforated Peptic Ulcer by Age*

Decade	Total Patients	Deaths	Operated	Deaths	Nonoperated	Deaths
10-19	1	0	1	0	0	0
20-29	20	1	19	0	1	1
30-39	27	1	26	1	1	0
40-49	44	4	41	2	3	2
50-59	35	8	30	5	5	3
60-69	28	7	25	5	3	2
70-79	19	8	15	4	4	4
80-89	3	1	1	0	2	1
90-99	1	1	0	0	1	1
Total	179	31	159	17	20	14

TABLE 6.—*Time Interval Between Perforation and Surgery*

	No. of Patients		Deaths
0-6 hours	75	75.4% of total	3
7-12 hours	45		4
13-18 hours	12		2
19-24 hours	10		3
Over 24 hours	10		5
Unknown	7		0
	159		17

with the lapse of time between the onset of the symptoms of perforation and surgical intervention. Approximately 75% of the patients were operated upon within 12 hours of the onset of the symptoms of perforation. There were 7 deaths in the group of 120 patients operated upon under 12 hours of onset of symptoms. Approximately one-quarter of the 39 patients operated upon after 12 hours died (Table 6).

Significant Concomitant Disease.—Significant concomitant disease was present in 29% or 9 of the 31 fatalities. In only 3 of the 17 fatalities in the operative series was there a serious coincidental disease, while in 6 of the 14 nonoperative fatalities did this occur. In some instances the presence of a serious concomitant illness played a role in the preference for nonoperative treatment over surgical intervention.

Postoperative Complications.—Postoperative complications accounted for the death in nine, or over one-half of the operative fatalities (Table 3). Two patients died of bronchopneumonia, and one each from pulmonary embolism, asphyxia due to aspiration of gastric contents, peritonitis due to leakage following closure of the ulcer, peritonitis from a second rupture, massive hemorrhage from the closed ulcer, overwhelming septicemia, and a subphrenic abscess leading to a terminal peritonitis.

Errors in Diagnosis.—Five of the 14 patients, not operated upon, who died were in extremis at the time of admission to the hospital and died within a short time. The correct diagnosis was not made in any of the remaining nine patients not operated on. No adequate explanation can be given for these clinical failures. Such instances must be recognized as an important factor in the continuing relatively high mortality associated with acute perforation of peptic ulcers and should remind the surgeon again of the responsibility he assumes when he does not operate upon the patient with acute abdominal symptoms. Here lies a key to possible improvement in our results. If these nine cases in which the diagnoses were not made could be excluded from the series, the over-all mortality would be 13% instead of 17.3%.

Clinical Shock.—In approximately 10% of the total series a clinical diagnosis of a shock-like state was made by the admitting physician. In the 31 hospital fatalities, 12, or approximately one-third, exhibited clinical evidence of shock. Of the 17 operative fatalities, 8, or approximately one-half of the patients, had a clinical diagnosis of shock made on admission as evidenced by hypotension and tachycardia. Of the 14 nonoperative fatalities 4 patients were considered to be in a shock-like state on admission.

Comment

A critical analysis of 179 consecutive cases of acutely perforated gastroduodenal ulcer at the Buffalo General Hospital over the 15-year period from Jan. 1, 1942, to Jan. 1, 1957, revealed no appreciable improvement in the hospital mortality rate. The increasing use of chemotherapeutic and antibiotic agents during the period of study did not alter the mortality rate or the incidence of postoperative complications. From an analysis of this series of cases one can make a few observations concerning the factors that may play an important role in influencing the hospital mortality from acutely perforated peptic ulcers. In this series the age of the patient contributed to a rather high mortality rate in that the average age of all the fatal cases was 12-14 years greater than the average age of the survivors (Table 7). Furthermore, 80% of all fatalities occurred in patients 50 years of age or older.

TABLE 7.—*Age of Patient with Perforated Peptic Ulcer*

	All Patients (Approx. Aver.)	Surviving Patients (Approx. Aver.)	Deaths (Approx. Aver.)	
			Operative	Nonoperative
1942-1946	50	48	60	61
1947-1951	48	45	57	66
1952-1956	52	50	63	60
Total	50	48	60	62

The increasing death rate with increased time between the onset of the symptoms of the perforation and surgical intervention has been well established in many other reported series and is again emphasized in this series. In this series, operation within the first 12 hours of perforation carried a mortality rate of approximately 6%, whereas more than a quarter of the patients operated upon after a delay of more than 12 hours died. With a fourfold increase in the surgical mortality rate when the operation is delayed for more than 12 hours, it behooves the physician to establish the diagnosis early and institute immediate appropriate therapy to patients with a suspected perforation of a gastroduodenal ulcer. Patients with a serious coincidental chronic disease can be expected to have a higher mortality rate. However, in this series the influence of a significant concomitant disease on the mortality rate was minimal. A major factor contributing to the relatively high mortality rate of the operative cases is the high incidence of postoperative complications. In this series there were 42 complications in 40 patients, 9 of which were fatal. A reduction in the incidence of postoperative complications would substantially reduce the operative mortality rate. In a total of 179 cases of perforated gastroduodenal ulcer, the diagnosis was not made in 9 (5%) of the patients. Here both surgeon and internist must share the responsibility. Five patients never had the benefit of a surgical consultation, and in one case consultation was unduly delayed. The presence of clinical evidence of a shock-like state may be a factor contributing to the disappointing mortality rate in this series. Approximately one-half of the operative fatalities were considered, by the admitting physician, to be in shock.

A substantial reduction in the hospital mortality rate from acutely perforated gastroduodenal ulcers can only be accomplished by the acute awareness on the part of the internist and surgeon of the factors contributing to these fatalities. The marked increase in the hospital mortality associated with undue delay in the institution of appropriate therapy, be it due to failure to arrive at the correct diagnosis, lack of consultation, or delay in operating upon the patient with the signs and symptoms of an acute abdomen, emphasizes the tremendous responsibility the internist or surgeon must assume in caring for patients with suspected gastroduodenal perforations. Since the operative mortality increases hourly, it seems that hourly reappraisal of the patient with a suspected acute abdomen should be mandatory in order to establish an early diagnosis and early surgical intervention. The high incidence of postoperative complications, which in this series accounted for one-half of the operative fatalities, can be materially reduced by preventive measures, early recognition, and aggressive therapy of the complications when they occur. Certainly a reduction in the incidence of postoperative complications would substantially reduce the operative mortality rate. The fact that a large number of acutely perforated gastroduodenal ulcers occur in the older age group where there is a higher incidence of concomitant serious chronic illness means that closer management of the patient by the combined efforts of the surgeon and the internist should reduce the mortality in this area. The observance of a shock-like state in one-half of the operative fatalities and in one-third of all hospital fatalities indicates that more aggressive preoperative preparation with fluids, whole blood, and other supportive measures without unduly delaying surgical intervention should result in a lowering of this disappointingly high mortality rate.

Summary

One hundred seventy-nine consecutive cases of perforated gastroduodenal ulcer over a 15-year period have been critically studied. From this study it is apparent that no improvement in the mortality or morbidity has occurred in the years from 1942 through 1956. The primary factors influencing the mortality rate in this series appear to be the following:

1. Age of the patient
2. Time interval between the perforation and surgery
3. Postoperative complications
4. The presence of a serious concomitant disease
5. Errors in diagnosis
6. The presence of clinical evidence of a shock-like state on admission

Many of the factors contributing to the sustained death rate from perforated gastroduodenal ulcers are directly under physician surveillance and control. An awareness of these factors and a more aggressive treatment of patients with a perforated peptic ulcer will materially reduce this high mortality rate.

177 Beard Ave.

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DISCUSSION

DR. JOSEPH E. HAMILTON, Louisville: I was very much interested in the very interesting analysis made by Dr. Egan and his associates. I would like to raise some points in behalf of immediate elective surgery for these patients.

In 1956 Dr. Blain Lewis, of our Center, reviewed our results in the treatment of 183 consecutive cases of perforated ulcer at the Louisville Veterans Administration Hospital from 1946 to 1955. Of these, 178 were treated by simple suture, with an operative mortality of 2.3%, the total mortality being 3.8%.

[Slide] However, my associate, Dr. Phil Harbrecht, recently made a 3- to 12-year postoperative survey of the 146 traceable patients in this series after excluding the 5 postoperative deaths, 8 subsequent deaths due to causes other than ulcer, and 13 lost to follow-up.

He found that only 26% were well or mildly symptomatic, another 25% had moderate to severe symptoms and were still on medication, and 49% were total failures requiring reoperation.

Further analysis revealed that of those with severe and protracted symptoms before perforation, 65% later came to definitive surgery, and that 40% of even those with mild brief disease subsequently required reoperation. Another 20% in both categories had moderate to severe active disease after simple closure of their perforation.

We are therefore coming to apply initial definitive surgery to all patients in reasonable condition and without purulent peritonitis who have established disease or moderately severe disease. So far, 4 patients have undergone subtotal gastrectomy and 12 patients vagotomy and an emptying procedure, usually pyloroplasty. There have been no deaths or severe complications and no cases of demonstrable mediastinitis. We note that both Berne and Pierendosy and their co-workers also favor vagotomy, and report no severe complications or mediastinitis.

In our hands vagotomy plus an emptying procedure has proved as curative in chronic duodenal ulcer as a two-thirds gastric resection, has a significantly lower mortality than the subtotal, and leaves the patient his stomach. For this reason we are coming to favor this procedure in acute perforations also, especially as it is well suited to performance in the wee hours.

DR. WILLIAM H. REMINE, Rochester, Minn.: Since approximately 50% of patients require further surgery for perforated duodenal ulcer, we have recently embarked in a program of primary resection in the highly selected patient. I would like to emphasize that these are very highly selected.

To date we have done 14 of these with primary resections, without any loss of patients and without any increase in morbidity.

DR. WILLIAM T. MCELHINNEY, Covington, Ky.: Dr. Max Zinninger and I gave our statistics on perforated peptic ulcers treated at Cincinnati General Hospital before this Association in 1950.

[Slide] I am taking the cases from the 1945 to 1949 period because at that time we had added penicillin to the armamentarium of treatment. Our operative mortality at that time was 4%—122 patients operated upon, with 5 deaths. The nonoperative mortality was 50%—6 patients not operated upon, with 3 deaths. A total of 128 cases were treated, with 8 deaths—a 6.2% mortality. However, we found that we had an over-all hospital mortality of 18%.

[Slide] In checking the cause of death in this group we found that one was due to a hemorrhage from turned-in ulcer. Another was a ruptured thoracic aneurysm. There were two cases that had marked cirrhosis, and one had advanced pulmonary tuberculosis.

[Slide] I checked our cases from 1949 through 1958. At the 1950 meeting it was suggested that immediate gastric resection should be added in certain selected cases. This slide represents 213 cases, 156 with simple closure, 17 gastric resections, with 7% mortality. There has been one death in the gastric resection cases, in one with perforation associated with hemorrhage. In the nonoperative cases the mortality has been 67.5%.

As in the Buffalo series, many of these cases were not seen by a surgeon, and have had no surgical advice.

[Slide] In spite of our method of treatment, and in spite of adding immediate gastric resection in selected cases, since 1949, our hospital mortality for perforated peptic ulcer remains at 18%. Dr. Baritell and others have reported a 1% mortality; but in the over-all picture of perforated peptic ulcer the mortality is much higher in our hands.

In conclusion, I feel our bad results are influenced greatly by the type of patients we see, their age, and their associated illnesses.

Dr. Campbell Gardner, Montreal: As I understand emergency surgery, it should be emergency surgery only. We learned this during the war through bitter experience.

If one advocates a definitive procedure for an emergency condition, I believe one embarks often on a perilous course. Undoubtedly in the hands of an expert gastrectomist or vagotomist, definitive surgery *may* be justified in some cases, but I believe it is dangerous teaching.

My own feeling is this: If I have a perforated ulcer, please do not leave me in the hands of either of the above experts. I wish to have my ulcer closed (thank you) and have it dealt with at a later date if my symptoms recur.

Dr. John R. Paine, Buffalo: Gentlemen, certainly we are not proud of our results. We have had this information available for 18 months. We were ashamed to publish it, but our surgical conscience, Mr. President, finally prevailed upon us and we decided that probably we should bring this skeleton out of our closet.

We were somewhat encouraged in this also by noting that a similar series of about the same size at another teaching hospital in Buffalo had practically the identical mortality.

I was glad to hear Dr. Gardner's comments. He lends me a lot of moral support in something I have been unable to accept; yet with these figures one wonders what one should do about it. It just does not seem logical to me that if a patient with peritonitis will withstand having his ulcer closed, he will withstand better having his stomach removed. Maybe we will come to that, but I would vote with Dr. Gardner, at least at the present time.

I think it is fair to say that there were 46 surgeons who had to do with the treatment of these patients, and I do not doubt but that a series treated by a few select surgeons would certainly show a better mortality rate.

One inference you might draw is that we do not know how to treat a peptic ulcer in Buffalo. That is your privilege. On the other hand, if you will honestly and critically look at your own figures, I think many of you will be surprised that you have not made the progress during the last 15 years you think you have made in the treatment of this very common illness.

The Surgical and Nonsurgical Treatment of Gastric Ulcer

An Analysis with Special Reference to the Incidence of Cancer

ROBERT E. L. BERRY, M.D., Ann Arbor, Mich., and LEWIS A. SCHMIDT III, M.D., Chattanooga, Tenn.

The treatment of gastric ulcer that does not possess characteristic appearance of malignancy by x-ray, gastroscopic examination, or cytological washings has sustained a continuing controversy that at one extreme will have those who state dogmatically, "All gastric ulcers should be resected," and at the other a massive stoic conservatism against surgical excision. Surgeons and gastroenterologists only too often infer that their therapeutic domain has been trespassed upon by the other. Usually both groups are quite capable of substantiating their position by citing instances, on one hand, of far-advanced gastric malignancy attributed to prolonged attempts at conservative treatment and, on the other, to "unnecessary operations" because of failure to demonstrate malignancy in tissues removed by gastric resection.

The pivotal point of this argument rests upon the lack of absolute reliability of any diagnostic procedure except carefully studied microscopic serial sections of the diseased area. Until such time as the diagnosis can be unequivocally made without excision of the ulcer, a substantial difference in opinion regarding the routine use of gastrectomy for all gastric ulcers will continue to exist.

In an attempt to obtain a clearer perspective of this problem, an analysis of the treatment of *all* gastric ulcers was undertaken, regardless of whether or not gastric resection was necessary and with the principal orientation being, "was this equivocal ulcer benign or malignant?" At this clinic the majority of gastric ulcers of this type have been treated by a conservative medical regimen for a minimal period of three weeks. This has permitted observations to be made on the results of conservative management as well as the incidence of cancer in specimens resected because of suspicion of malignancy due to failure of the ulcer to "heal."

Material

Four hundred fifty gastric ulcers, seen at the University of Michigan Hospital during the 11-year period Jan. 1, 1940, to Jan. 1, 1951, were chosen for this study. All were approximately 2 cm. in diameter or smaller in size. It should be emphasized that this is a highly selected group and is made up of two types of cases: (1) gastric ulcers treated medically with and without successful results but not operated on, and (2) gastric ulcers submitted to resection because failure to adequately respond to conservative management made them suspect of cancer. This series does not include operations done for hemorrhage, obstruction, perforation, intractability, or lesions in which the diagnosis of cancer was felt initially to be reasonably obvious.

The principal diagnostic modality, as well as evaluation method for response to treatment, was the x-ray. Gastroscopy and gastric cytology studies, although utilized extensively as diagnostic procedures in recent years, had limited application to the chosen study period. A minimum of five-

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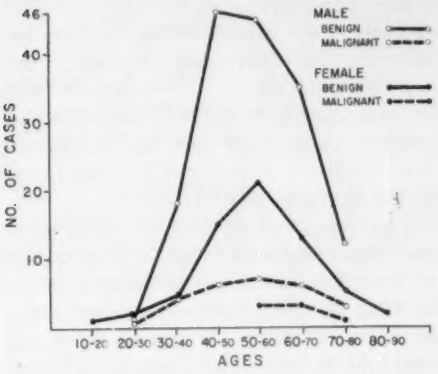
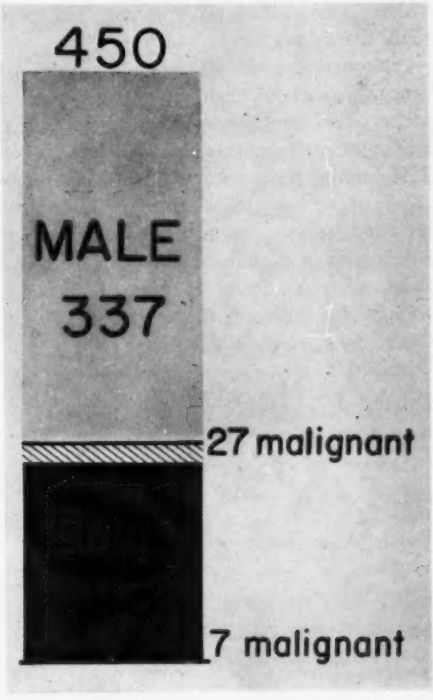


Fig. 1.—Incidence by age groups and sex of 450 gastric ulcers of an equivocal type. All ulcers were approximately 2 cm. or less in size. Three times as many males as females were found, but the incidence of cancer in male patients approached a 4:1 ratio.

Fig. 2.—Distribution by sex of 450 gastric ulcers and the incidence of benignancy and malignancy determined by a minimal five-year follow-up. The majority of cancers in this "equivocal" group were in males and in the approximate proportion as for all cancers of the stomach.



year follow-up has been permitted by closing the series in 1951.

Results

Age and Sex.—In this series, the incidence of gastric ulcer, whether benign or malignant and regardless of sex, was more prevalent in the fifth, sixth, and seventh decades. Three times as many males (337) as females (113) were found in the over-all series but the incidence of cancer

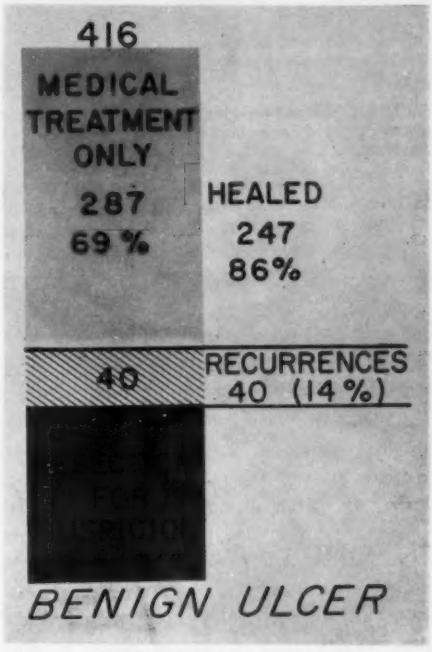


Fig. 3.—Results of early conservative treatment of 416 gastric ulcers subsequently proved to be benign. Satisfactory results were obtained in 55% of cases by "conservative" methods. A failure of medical treatment was observed in 45%. Of the total 450 ulcers in the series, 34 were malignant (8%).

was relatively greater in men (27) than in women (7) (Figs. 1 and 2).

Incidence of Benignity and Results of Conservative Treatment.—Of the total 450 gastric ulcers, 416 (92%) have been demonstrated to be benign. It has been assumed that this observation is correct because of failure to develop cancer during a minimum follow-up period of five years or known

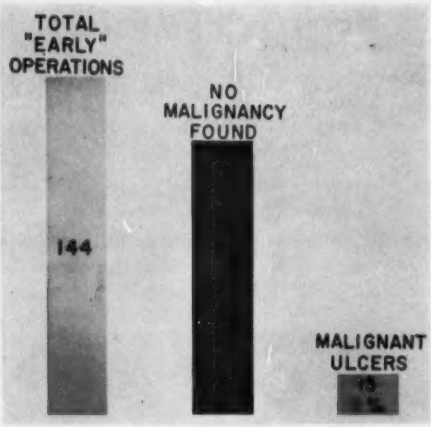


Fig. 4.—Incidence of malignancy in gastric ulcers removed early because failure to heal made them suspect of cancer. This figure increases to 17% if late failures to heal are included. If all cancers had been resected, the incidence would have been 21% in the resected specimens.

death from other causes. Under conservative management 287 ulcers "healed" (64%). Of these, 247 (86% of the "healed" group) demonstrated no recurrence. There were one or more recurrences in 40 cases (14%) without subsequent resection (Fig. 3).

Results of Early Operative Treatment.—"Early" operation was performed in 144 cases because of failure of adequate healing during an observation period under a rigid conservative regimen (Fig. 4). No cancer was found in 129 patients (89%). Fifteen malignant lesions were resected (11%). Of these, 12 were operated upon in less than two months after diagnosis. One is still living after 10 years. Three patients lived more than five years and died of other causes than cancer. One died between four and five years postoperatively without recurrence. The others died of cancer. Five-year survival rate (also cancer-free rate) of this group is 42%. Three other patients operated on between four and six months after diagnosis were all dead from cancer in less than two years (Table 1).

The Incidence of Cancer.—Thirty-four carcinomas were eventually demonstrated in these 450 patients, an absolute incidence of 8%. In addition to the cancers found at "early" operation, 11 other patients had their ulcers "healed" on conservative management, only to return, usually within a year, with advanced malignant disease. In only five of these patients could the cancer be resected. One is alive more than 10 years after operation; the remainder are dead of their disease. One patient, however, survived more than five years without operation.

The remaining eight patients either refused operation or otherwise "escaped" surgical treatment. All are dead from cancer. Of this group, three patients survived more than five years.

Although the demonstrated incidence of cancer in early operations was 11%, if all cancers had been resected, the incidence of malignant involvement would have been 21% in the removed specimens. If the 40 cases of recurrence of benign disease are included in this computation, then the incidence of malignant disease in "medical failures" would be 17%. These figures are compatible with those of previous authors.[7,9,10]

TABLE 1.—*Periods of Survival for Thirty-Four Malignant Ulcers*

Operation	Survival, Years						
	Less Than 1	1-2	2-3	3-4	4-5	5-10	10+
Less than 2 months (12)	2	2	2	1	1*	3*	1*
4-6 months (3)	1	2					
"Healed" — subsequently demonstrated to be malignant (11)	3	1	(2)	1	1	2	1*
Failure to heal in 2 months — no operation (6)	2	2	1			1	
Healed — late development of cancer (2)						2	

* Living or died of other causes than cancer. The numbers in parentheses represent those known to have cancer, but the time of survival and cause of death are not known, although they did live less than five years.

Operative Mortality: There were seven deaths in 129 resections for benign disease, a mortality of 5.4%. Two additional deaths followed resections for malignant disease, a resultant over-all mortality of 7% for 149 operations in this series.

Comment

Statistics related to the problems imposed by gastric ulcer are notoriously vague, confused, and subject to a wide range of interpretation. Apparently about 40% of gastric resections are done for suspicion of cancer, another 40% because of intractability or recurrence, and the remaining 20% because of hemorrhage, obstruction, and perforation.[7] As previously emphasized, this paper is concerned only with the problem of gastric cancer in those ulcers that mimic benign disease and in no way is intended to include other indications for operation or to discuss the comparative morbidity of medical and surgical treatment.

That the conservative management of the type of gastric ulcer included in this study is worth while is difficult to refute. Of 450 ulcers, 247 (55%) went on to complete healing under conservative management. For these patients this was the proper treatment. Enough time has passed to demonstrate that "immediate" gastrectomy indeed not only would have been an unnecessary operation but would have exposed these patients to the attendant morbidity and potential mortality. The remaining 45% of this group, however, (1) had recurrence of their disease but were not submitted to gastric resection, (2) underwent resection because of failure to respond to treatment, or (3) subsequently were demonstrated to have malignant growths.

The percentage of failures of the medical treatment of gastric ulcers varies considerably and has been quoted[4,5] at 33%-98%. Obviously different authors are using variable yardsticks as the estimate of failure. Despite an apparent over-all 45% failure for conservative treatment, recurrent ulceration in benign disease not submitted to surgery was only 14% in this series (Fig. 3). This figure is lower than other reports and could conceivably be due to the high selectivity of cases.[4-6]

An over-all incidence of 8% of malignant ulcers essentially confirms previously reported figures.[1,7,9,10] Any lesion that possesses almost a 10% incidence of malignancy can be reasonably rationalized as an indication for immediate operation by those who feel that a period of conservative treatment represents little but an unjustifiable delay.[14] The situation becomes even more ominous when it is realized that if all carcinomas could have been removed, the incidence of malignancy in the resected specimens of this series would have been 21% (Table 2). This is not the entire problem, however.

TABLE 2.—*Statistical Components of Varying Approaches to Ulcer-Cancer Problem* *

Over-all incidence of cancer	34/450	8%
Incidence in "early" resected specimens	15/144	11%
Incidence in all resected specimens	20/149	13.5%
Incidence if all "recurrent" benign ulcers were resected	34/203	17%
Incidence if all cancers had been resected	34/163	21%

* Such statistics are notorious for their vagueness and ambiguity.

Of the subsequently proved 34 malignancies only 20 came to gastric resection. Of these, 12 were done in two months or less after the diagnosis of gastric ulcer. Four patients died having survived periods of approximately five years or longer and represented a five-year survival rate of almost 42%. Although compatible with previous observed rates,[1,9] the number of cases is so small that for this group percentage is meaningless.

A particularly disturbing group is represented by 11 cases that "healed" under conservative therapy, only to return, usually between 8 and 12 months, with obvious cancer. Resection was possible in five cases. One is still alive without disease after 10 years. One lived more than five years after operation and then succumbed to cancer. The remainder are all dead. Although small

in number, this type of case has convincingly demonstrated that carcinomatous ulcers may give all the appearances of "healing" during a period of conservative treatment, and therefore represents one of the weakest links in the conservative treatment chain. The delayed appearance of cancer in an apparently "healed" ulcer is a well-recognized occurrence and necessitates ceaseless observation of all conservatively treated gastric ulcers for a period of at least two years if this type of cancer is to be detected.

Patients with carcinoma who refused operation or otherwise "escaped" surgical treatment are all dead of their disease. Three cases, however, survived for more than five years without operation and then died of carcinoma. Of two patients classified as "insufficient data" it is known that they had cancer of the stomach, but the exact cause of death has not been identified, although it is known that both lived less than five years after the diagnosis was made (Table 1).

Stout has identified a certain group of gastric cancers as superficial spreading carcinoma.[2,11-13] This group includes lesions previously described as carcinoma in situ and makes up about 8.3% of all stomach malignancies. Approximately 87% are characterized by "peptic ulceration." Grossly these lesions may appear as a thickened hyperemic mucosal layer with slight superficial irregularity or nodularity but possess no characteristic neoplastic features. Direct inspection and even frozen section may contribute little to the accurate diagnosis. Microscopically these lesions can be confined to the mucosa and adjacent submucosa. The base has a proliferative fibrosis with chronic inflammatory infiltrations and no evidence of neoplasm. The mucosa demonstrates foci of neoplastic cells both near and at a more remote site from the ulcer. Ulceration may penetrate the whole wall. This rarely occurs in any other form of gastric carcinoma. The superficial location, however, is accompanied by a 50% lymph node metastatic incidence (Stout), and although the survival rate is low it is definitely above average.

TABLE 3.—*Five-Year Survival Rates Following Gastric Resection for Malignant Ulcer*

Early operation	5/12	41%
Resected cancers	7/20	35%
Nonresected cancers	4/14	28% *
All cancers	11/34	33%

* Even though the number is small, a 28% survival for nonresected cancers is highly suggestive of the low biological malignant potential of many ulcer-cancers.

Dockerty has observed that lesions less than 2.5 cm., mimicing benign gastric ulcer, have an unusually good prognosis.[3] The incidence of nodal spread is only 15% and a five-year survival rate of almost 60% has been observed.

Despite the small number of malignancies in this series, they appear to add substance to the observation that the prognosis of ulcer-cancer of this type is considerably better than cancer of the stomach in general. Whether or not this is due to "early operation" or is related to the inherent biological malignant potential and host resistance of such cancers cannot be accurately assayed in this series. The over-all five-year survival rate for the 34 malignancies was 33%. For those who submitted to gastric resection, including both early and late resections, the survival rate was 35%. Both survival rates are obviously higher than generally quoted statistics for cancer of the stomach (Table 3).

On the other hand, however, in the search for cancer nine patients died in the immediate postoperative period (Table 4). Of those undergoing resection, seven survived five years or longer. Is the treatment

TABLE 4.—*Immediate Postoperative Mortality Rates for Benign and Malignant Gastric Ulcer* *

Benign ulcer	5.4%
All resections	7.0%
Resected patients surviving 5 years	7
Postoperative deaths	9

* Although the number of deaths are greater than the 5-year salvage, in no manner should it be concluded that the operation of gastric resection is invalidated (see text).

worse than the disease? Jordan has stated that the mortality rates from the medical and surgical treatment of gastric ulcer are approximately the same.[7] The postoperative mortality rate in this series is admittedly higher than usually reported for gastric resections of this type [7] but is not unreasonable when compared with training centers with similar type of patients.

Even if maximum slant is placed upon such a small series, the equality of five-year survivals and postoperative deaths could hardly invalidate the operation as effective treatment for the following reasons:

1. Statistics cannot be applied to a given patient. Each case must be evaluated upon its own merits. If there is one five-year survivor after resection, then any given case could potentially represent another five-year "cure," and for that patient the operation represents a 100% survival. Furthermore, even though no cancer is found, resection will obviate the inevitable percentages of conservative therapy morbidity and emergent surgery.[6,14]

2. All cases of ulcer-cancer are not of low biological malignant potency. Even though the total group demonstrates a 33% five-year survival, certain of these patients survived less than three years. Their only hope is early surgical excision, although full cognizance must be given to the consideration that the prognosis is importantly related to the biology of the tumor and host resistance as well as the scope and timing of the operation.[8]

From this study can any information of value be obtained to aid in resolution of controversial problems of the management of the equivocal gastric ulcer of approximately 2 cm. or less in diameter at the time of initial diagnosis?

1. Of the total series, 55% responded adequately to conservative management and from obtainable information have remained healed.

2. Recurrence in nonoperative benign ulcer, resection for suspicious lesions demonstrating inadequate healing and malignant ulcerations have been grouped together as "medical failures" and represent 45% of the series.

3. Any treatment that has been 55% effective as related to the nature of the disease and the circumstances of this study, would support the contention of those who maintain that a period of closely supervised medical treatment should initiate the therapeutic program of these patients.

4. A small number of patients, probably less than 3%, will apparently "heal" their malignant ulcers under conservative management. All patients being treated conservatively should be closely watched for a period of at least two years. Despite the delay in operation 3 out of 11 patients in this group survived five years or more.

5. It would appear that this type of ulcer-cancer has a better prognosis than other forms of gastric malignancy. The best results have occurred when operation was done earliest. Care should be taken, however, in ascribing a higher percentage of survival to early operation without thoughtful consideration that this type of gastric cancer probably has a higher incidence of low biologic malignancy with attendant greater host resistance and that survival rates are more pertinently related to this consideration than to the "early" operation.

Summary and Conclusions

A series of 450 equivocal gastric ulcers approximately 2 cm. or less in diameter has been presented. The failure rate of conservative management was 45%.

The incidence of malignant ulcer was 8%. Five-year survival periods for malignant disease were as follows: early operation 41%; all cancers 33%, and nonresected cancers 28%.

From this limited number of malignancies, the evidence has suggested but cannot be interpreted as conclusive, that the improved prognosis of early resection of the type of malignant gastric ulcer included in this series is possibly more related to a lower malignant biological potential than to early surgical intervention.

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Correlative Study of Postgastrectomized Patients

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Several different operative procedures may be used in the treatment of ulceration of the duodenum or stomach with a very low ulcer recurrence rate. With the recognition of this fact, physicians have started to focus their attention on the undesirable sequelae of such operative procedures.

A consideration of postgastrectomy abnormalities should include recurrent ulcer, afferent loop syndrome, biliary regurgitation, efferent loop obstruction, hypoglycemia, anemia, early postcibal vasomotor symptoms, diarrhea, and undernutrition. The occurrence of these undesirable sequelae has been previously discussed.[1] While the presence or absence of all of these abnormalities was determined, this study is primarily concerned with early postcibal symptoms, diarrhea, and undernutrition.

The following conclusions were derived from a review of the rather extensive literature on postgastrectomy problems which has accumulated in the past several years.

1. The term "dumping syndrome" has a variety of meanings when used to describe postgastrectomy ailments. Although Mix [16] in 1922 was apparently the first to use the term "dumping stomach" to describe rapid gastric emptying in a patient with gastrojejunostomy, recently some authors have used the term "dumping syndrome" for all postgastrectomy problems whether due to obstruction, rapid gastric emptying, or abnormal afferent loop function, etc. In order to eliminate some of the confusion which surrounds the usage of this term, we believe that "dumping" should only be used to describe rapid passage of ingested material through the anastomotic stoma into the upper small intestine, whether it follows a gastroenterostomy, a partial or total gastrectomy, or whether or not it is combined with a vagotomy. By such a definition the term "dumping" should be reserved to indicate the excessively rapid emptying of ingested material into the upper small intestine and would not necessarily imply the occurrence of symptoms. While many of the reports are concerned with patients with total gastrectomy, this study is limited to patients with gastroenterostomy or partial gastrectomy with or without vagotomy.

2. The incidence of dumping reported by various authors ranges from as little as 1% [13] to as great as 75%.[10] These marked discrepancies are due to variations in the definition of "dumping," the methods used to ascertain the frequency with which it occurs, and the failure to recognize that some dumping patients are asymptomatic or learn to minimize or avoid symptoms by altered eating habits (avoidance of certain carbohydrate foods, small frequent feedings, and/or lying down during or after eating), which may result in a state of chronic undernutrition and/or anemia.

3. Numerous investigations concerning the etiology of the symptoms associated with dumping (weakness, warmth, flushing, sweating, nausea, vomiting, palpitation, fainting, or diarrhea) have resulted in a variety of theories. In the decade 1940 to 1950, four general approaches were used to explain the mechanism of the "dumping syndrome."

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A. Perman [18] suggested an insufficiency of the circulation mediated by nervous reflexes arising from the small intestine as the cause of the symptoms. Hoffmann [12] in 1939 had proposed in greater detail a nervous mechanism as the cause of symptoms. He postulated that the rapid entrance of food into the intestine led to a pooling of blood in the splanchnic area mediated through the autonomic nervous system with a resultant decrease in cerebral blood flow. This theory was supported in general by the Scandinavian workers, including Bruusgaard [4] and Boman.[3] The relief of dumping symptoms by lumbar sympathetic block [6] and the intravenous administration of a sympatholytic drug [15] may be cited in support of Hoffmann's hypothesis implicating the autonomic nervous system as the precipitating mechanism in the occurrence of symptoms.[12]

B. Mechanical factors were proposed as the cause for symptoms by various investigators. Butler [5] and Capper [7] believed distention of the gastric remnant and gastric stretching by the weight of a filled afferent jejunal loop produced the symptom complex which they believed was probably mediated through the sympathetic nervous system. While patients with these mechanical abnormalities may exhibit symptoms which are somewhat similar to the vasomotor symptoms of the "dumping patient" (rapid gastric evacuation) the latter patients do not exhibit gastric distention or afferent loop stasis by x-ray studies.

Other workers, including Adlersberg and Hammerschlag,[2] proposed that the dumping syndrome resulted from mechanical factors associated with a small gastric pouch. This theory is untenable in view of the fact that the dumping syndrome was noted [16] and occurs not infrequently [1] in patients with gastroenterostomy and an otherwise intact stomach.

Machella [14,15] demonstrated that mechanical distention of the small intestine by an inflated balloon produced epigastric discomfort, anorexia, palpitation, and occasionally other symptoms. While intestinal distention may account for some of the symptoms noted in the dumping patient, it does not explain the decrease in plasma volume or diarrhea frequently observed in these patients but may be the cause of epigastric or periumbilical pain, anorexia, and palpitation.

C. Glaessner [9] in 1940, and Gilbert and Dunlop [8] in 1947 attempted to relate the dumping syndrome to changes in blood glucose concentrations. The former believed that the early hyperglycemia was the cause, while the latter implicated the late hypoglycemia which occurs in an occasional patient. These theories were refuted by a number of investigators, and the evidence against them can be summarized by the facts that the symptoms cannot be produced by an intravenously established hyperglycemia, and if hypoglycemia occurs it is noted one to two hours after the early postprandial or dumping symptoms.[14,15]

D. Machella [14,15] demonstrated that dumping symptoms can be produced in a normal person by the introduction of different hyperosmolar solutions directly into the small intestine (via a tube), which may explain the symptoms in many of the patients with rapid emptying of the gastric contents into the small intestine. Subsequent reports by Roberts, Randall, and Farr [19] lend support to this belief. They demonstrated that a plasma volume deficit may occur because of a translocation of extracellular fluid into the intestine.

The present study was undertaken in order to determine why some patients with rapid gastric emptying are symptomatic while others are asymptomatic. Specifically the purpose of this study was to comprehensively investigate a group of patients who had undergone some type of operation for the treatment of benign gastric or duodenal ulcer in an attempt to clarify some of the reasons for the variations in occurrence and magnitude of symptoms in these patients. The following studies included the use of previously described techniques, the introduction of new tests, and

a comparison of the symptomatic patients with normal persons as asymptomatic patients who previously had a subtotal gastrectomy or gastroenterostomy with or without vagotomy. It was hoped that the data obtained from this study would clarify the frequency of dumping and further elucidate the mechanisms responsible for its occurrence. We also hoped to reexamine the hypothesis that the maintenance of a gastric "reservoir" by modification of the operative technique will avoid postgastrectomy abnormalities.[1]

Methods

Patients who had been operated upon for a duodenal or benign gastric ulcer since 1948 were considered for this study. Patients who had a gastric operation in the last six months were not studied, nor were those who had simple closure of a perforated ulcer or an operation for a gastric malignancy. The generally accepted indications for operation applied, namely, hemorrhage, obstruction, failure of medical management, and in some instances a suspicion of malignancy in a gastric ulcer. A variety of procedures are represented by this group of patients. The majority of the patients had a hemigastrectomy-gastroduodenostomy with a vagotomy or a subtotal gastrectomy with a gastrojejunostomy (Polya, Hofmeister, and other types of anastomoses). However, one or more patients who had the following procedures were also studied: partial gastrectomy with gastroduodenostomy, partial gastrectomy with gastrojejustomy and vagotomy. The study was divided into three parts: interview, roentgenographic studies, and special tests including dietary evaluation. Each patient was interviewed and had roentgenographic studies, and the majority underwent one or more of the special tests.

Interview.—Each patient was interviewed by one or more of us. In order to standardize the information obtained, a questionnaire was prepared which was used as a guide and provided a comprehensive inquiry into dietary habits, weight changes, and the occurrence of postprandial symptoms before and after operation. Additional questioning of the patients often occurred when they were admitted to the Surgical Metabolic Division of the University Hospitals of Cleveland for x-rays and other tests.

Roentgenographic Studies.—We have previously described a technique for appraising gastrointestinal function.[1] Briefly it consists of ingestion by the subject of a barium food mixture over a four-minute period and then the obtaining of serial x-ray films. Originally 75 gm. of barium sulfate was mixed in a blender with 60 ml. of orange juice, 60 ml. of coffee, one slice of toasted white bread, one pat of butter, and one soft-boiled egg. For the past year a barium chocolate milk shake (protein 19.5 gm., fat 11.3 gm., carbohydrate 46 gm., barium 70 gm., with a total volume of 330 ml.) has been used. This latter mixture is more palatable and equally satisfactory for the study. We have also found that the number of x-ray films could be limited to four or five and we could still obtain the necessary information. *Upright* 14×17 in. roentgenograms encompassing the abdomen and lower chest obtained at 1, 20, 45, and 90 minutes after the ingestion of the barium food mixture provided the desired information. (Previously films were obtained at 1, 20, 30, 45, 60, 90, and 120 minutes.) In most instances a survey film was obtained prior to ingestion of the mixture for proper positioning and to ascertain the presence or absence of fluid or air in the stomach. These roentgenographic studies were conducted in the morning after an overnight fast. In some instances when a similar study had been carried out previously, the reexamination afforded an opportunity for noting any changes in function that may have occurred with the passage of time. This roentgenographic study was used to determine gastrointestinal function in the patients and a group of normal volunteers. This examination was not used, nor should it be employed to determine the presence of an anatomical abnormality, but is a reliable method for estimating gastric emptying time and small intestinal transit time. When anatomic abnormalities such as peptic ulcer, hiatus hernia, tumor, etc., were suspected, a conventional upper gastrointestinal series was obtained. Fluoroscopic examination, manipulation, and changing the patient's position were not employed with the barium food study since this might alter gastrointestinal function.

Dietary Studies.—In order to evaluate actual daily caloric consumption, some of the patients were placed on weigh-back diets of their own selection (three regular meals plus extra nourishment) for three or four days. The caloric and fat values of the foods were calculated from dietary tables.[2] Several undernourished patients with dumping symptoms were studied for a three- or four-day period on a constant analyzed diet to estimate caloric consumption and to determine whether excess fat or nitrogen was present in the stool.

Challenge with Hyperosmolar Solution.—The majority of patients were given orally 2 ml. of 50% glucose solution (1 gm. of glucose) per kilogram of body weight to determine whether symptoms could be provoked in asymptomatic or symptomatic patients and to determine the exact

nature of the complaints if they occurred. This challenge was also used in an attempt to determine the physiologic differences which distinguish the symptomatic from the asymptomatic response in patients who exhibit rapid gastric emptying time by barium food x-ray studies. During the test, each patient was evaluated clinically (patient's complaints, changes in pulse, blood pressure, skin color, sweating, borborygmi, diarrhea, etc.), and in most instances changes in plasma volume and peripheral blood flow were also determined.

Plasma volume changes associated with ambulation and ingestion of 50% glucose solution were determined with radioactive iodinated albumin.[20] With the patient in bed and in a fasting state, 20μc of radioactive iodinated albumin diluted to a volume of 20 ml. was injected intravenously. A blood sample was obtained 10 minutes after the injection. During the next hour two or three blood samples were obtained. The patient then walked about for 15 to 30 minutes and sat in a chair for 15 minutes, after which time three more blood samples were obtained. While sitting in a chair the patient was then given orally the 50% glucose solution. Subsequently, a minium of three blood samples were taken. The total number obtained after the ingestion of the glucose solution was dependent on the development or absence of symptoms. When symptoms occurred, sampling was carried out at 5- to 10-minute intervals and at 15- to 30-minute intervals if symptoms did not occur or after their disappearance. The heparinized blood samples were collected in Sanford-Magath cell volume (hematocrit) tubes in order to determine hematocrit (per cent packed red cell volume) changes. A Cournand needle was placed in an arm vein in order to avoid repeated venipunctures. The control plasma volume was calculated from the 10-minute sample according to conventional methods.[20] The radioactivity of each plasma sample in counts per minute per milliliter of plasma was plotted against time on semilogarithmic paper, which provided a disappearance curve of radioactivity from the blood. Any change in plasma volume during the postingestion period was calculated from points which diverged from the expected disappearance curve projected from the preambulatory and preglucose ingestion slope.

Changes in peripheral blood flow following ingestion of 50% glucose solution were recorded with Winsor-Burch plethysmograph as described by Winsor[24] and utilized by Hinshaw and his associates.[21]

Results

Interview.—Although, the questionnaire we used as a guide was quite comprehensive, in many instances considerable discussion and explanation was necessary before it was established that the patient had symptoms referable to his gastric operation. It is well known that many patients who experienced considerable difficulty from their ulcer prior to operation tend to minimize postoperative problems because they are so gratified with the relief of periodic pain, dieting, bleeding, or vomiting.

A few of the patients who failed to gain weight postoperatively described representatively daily meals which were significantly deficient in both calories and protein. It was apparent from further questioning that such patients had established these eating habits in order to prevent the occurrence of unpleasant symptoms associated with larger intakes. These patients usually refrained from eating certain foods such as milk, milk products, and desserts rich in carbohydrates, which they found by experience elicted symptoms. In the majority of patients the cause for the weight changes and the occurrence and nature of symptoms could not be clearly elicited from the interview. This became apparent after observation in the hospital. A few patients were still following a semiulcer diet with frequent feedings because of the physician's warning that "now you have a small stomach and will have to eat small frequent meals." Others remained on an ulcer regimen because of their own or their physician's concern over the possibility of ulcer recurrence. Additional studies revealed that some of these patients were capable of eating a regular diet. Several patients (well exemplified by one who was recently studied) failed to disclose after extensive questioning that they experienced dumping symptoms especially when they ate foods with a high carbohydrate content. However, the latter patient noted that the symptoms which he experienced after ingesting the 50% glucose solution were the same as those which he had after eating certain foods rich in carbohydrate.

Roentgenographic Studies.—Figure 1 shows the serial roentgenograms of a normal

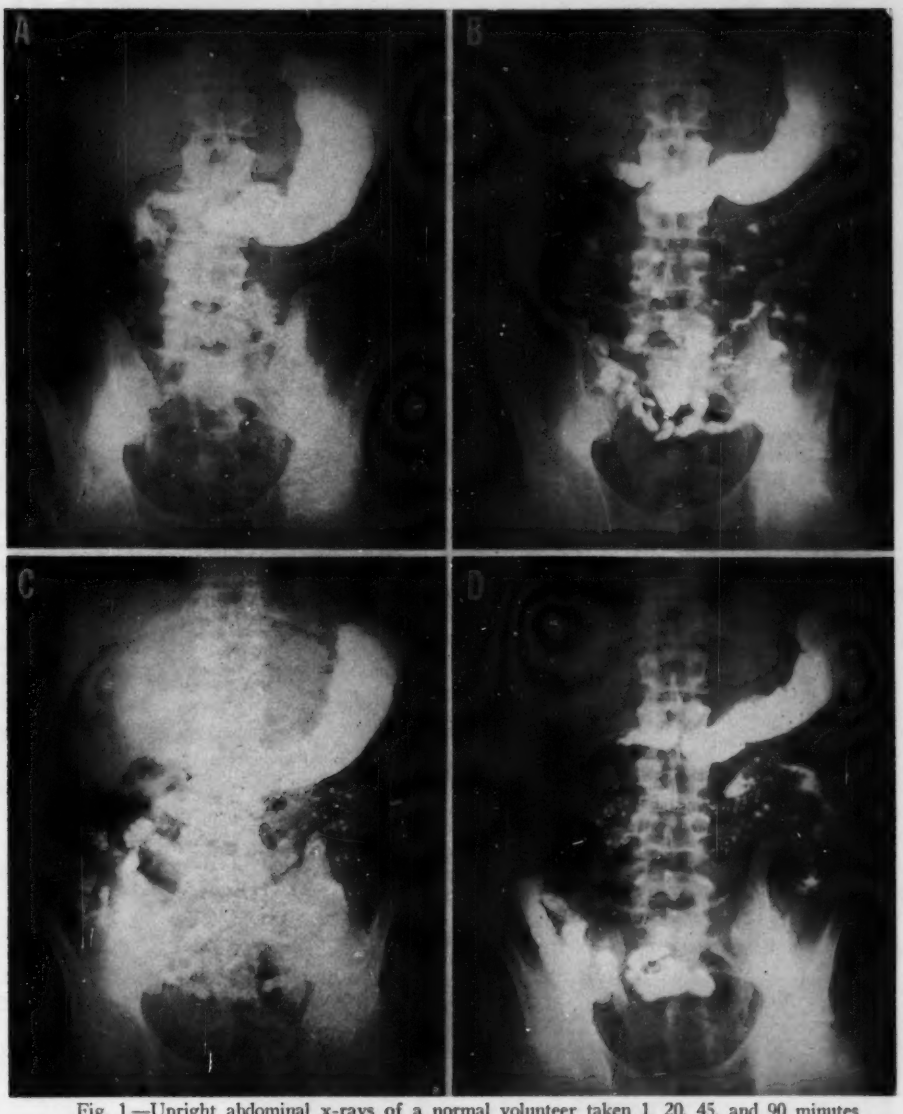

Fig. 1.—Upright abdominal x-rays of a normal volunteer taken 1, 20, 45, and 90 minutes after ingestion of the barium food mixture.

subject taken after ingestion of the barium food mixture. These are typical of those obtained from the group of normal volunteers who were studied by this and similar techniques.[1,17] It should be noted that one minute after (Fig. 1, *A*) the barium food mixture was completely ingested, essentially all of the barium remained in the stomach. The 20-minute film (Fig. 1,*B*) shows the head of the barium column in the terminal jejunum or proximal ileum and reveals that a considerable amount remains in the stomach. Because of the accumulation of gastric secretions, there has been a slight increase in the size of the stomach as compared with the first film. The subsequent

x-rays (Fig. 1, *C* and *D*), taken at 45 and 90 minutes, show that the barium food mixture gradually enters the small intestine, and a decreasing amount of barium and fluid remains in the stomach. Similar roentgenographic studies in healthy males and females showed that two hours or more was required for complete gastric emptying and that the head of the barium column had not entered the cecum by this time. These results were comparable to those noted by others [17] and were therefore used as a standard against which to compare similar studies in the patients.

All of the patients whom we studied who had a gastric emptying time faster than normal showed complete emptying within 45 minutes. Their rate of gastric emptying could be roughly correlated with the occurrence and magnitude of symptoms and undernutrition. The patients who showed complete emptying within one minute had the severest symptoms and undernutrition, and when their stomal size could be determined with certainty it was uniformly found to be 2 cm. or more in internal diameter. In many of these patients the head of the barium column had entered the cecum or ascending colon within 20 minutes. A few of these patients passed a liquid stool containing barium during the roentgenographic examination.

The x-rays shown in Figure 2 are from a 44-year-old, 114 lb. woman, who three years prior to the study had a very high subtotal gastric resection and a gastrojejunostomy for a benign gastric ulcer. This patient complained of postcibal nausea, palpitation, dizziness, sweating and faintness. These symptoms began 5 to 10 minutes after the onset of eating, were not related to the type of food, and were minimized after lying down. She gradually lost 20 lb. in weight after her subtotal gastric resection and had developed a moderately severe anemia, which had been treated and corrected by intensive parenteral therapy. It should be noted (Fig. 2, *A*) that five minutes after the beginning of the ingestion of the barium food mixture, the stomach is essentially empty and the head of the barium column is in the distal ileum. In the 20-minute film (Fig. 2, *B*) the barium column is in the ascending colon. Subsequent films are not shown because the patient passed a liquid stool containing barium prior to the 45-minute film.

Figure 3 shows x-rays which were taken of another patient 1 and 15 minutes after ingestion of the barium food mixture. The patient, a 37-year-old woman, had symptoms which were comparable to those of the preceding patient but had experienced a larger postoperative weight loss and disabling diarrhea. This patient had a large stoma gastrojejunostomy and vagotomy performed for a duodenal ulcer five years prior to this study. None of her stomach had been removed.

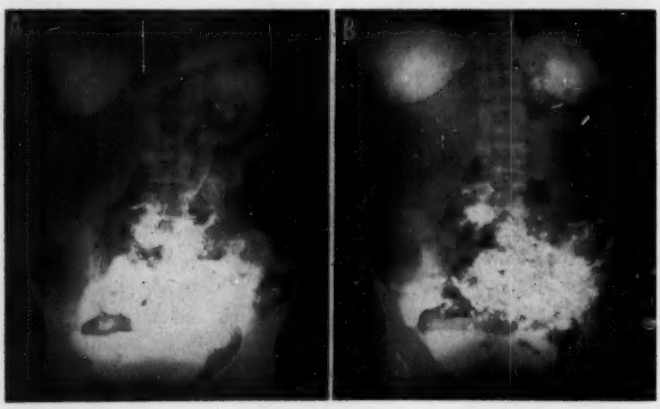

Fig. 2.—Upright abdominal x-rays of a 44-year-old woman taken 1 and 20 minutes after ingestion of the barium food mixture. She was a serve symptomatic dumper, who three years previously had a high subtotal gastric resection with a large stoma gastrojejunostomy.

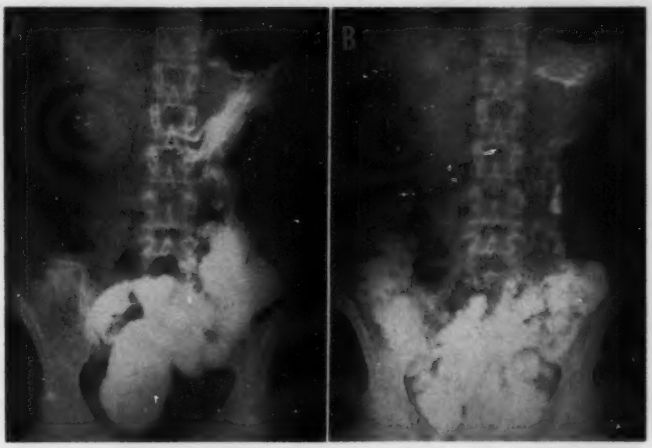

Fig. 3.—Upright abdominal x-rays of a 37-year-old woman taken 1 and 15 minutes after ingestion of the barium food mixture. She was a severe symptomatic dumper with intractable diarrhea, who five years previously had a large stoma gastrojejunostomy and vagotomy without resection.

Figure 3, *A* shows very little barium in the stomach and a considerable quantity in the distal small intestine, while Figure 3, *B* shows that barium has already reached the ascending colon. This film was taken at 15 minutes because of the patient's desire to defecate. Shortly thereafter, she passed a liquid stool containing barium.

The group of patients who had a hemigastrectomy vagotomy with a small stoma (less than 2 cm.) gastroduodenostomy or gastrojejunostomy exhibited essentially normal gastric emptying and small intestinal transit times. In the early postoperative period a few of these patients has a temporary partial stomal obstruction, which was manifest by the patients inability to take a full diet. When x-rays with the food barium mixture were carried out at this time, these patients exhibited a dilated gastric remnant with stasis and a very slow passage of barium from the stomach. All of these patients were able to take a normal diet within two to four weeks. Subsequent x-ray studies of these patients revealed that the barium emptied from the stomach and passed through the small intestine during a period of time comparable to that seen in the normal volunteers. Usually the very large dilated gastric remnant had decreased in size in spite of the fact that there was persistent stasis of fluid. A few of these patients had regurgitation, especially at night, and halitosis which disappeared in a few months.

Figure 4 shows the films taken at 1, 20, 45, and 90 minutes after ingestion of the barium food mixture. This 37-year-old man had a hemigastrectomy vagotomy with a small stoma gastroduodenostomy. The roentgenograms show a gradual decrease in the amount of barium in the stomach and an essentially normal small intestinal transit time.

The x-rays shown in Figure 5 were taken one minute after ingestion of the barium food mixture. This 51-year-old man also had a hemigastrectomy vagotomy with a small stoma gastroduodenostomy. Figure 5, *A*, which was taken nine days postoperatively, shows a markedly dilated gastric remnant. The barium gradually left the stomach, although there was not a significant decrease in the size of the gastric pouch during the next 1½ hours. The patient was eating well in spite of the gastric retention noted in the x-rays. Figure 5, *B* is a one-minute film taken seven months later, showing a considerable reduction in the size of the gastric remnant. Serial films at this time showed essentially normal gastric emptying and intestinal transit time. During this seven-month period the patient gradually gained to a normal weight. His halitosis and occasional regurgitation of gastric contents disappeared after several months.

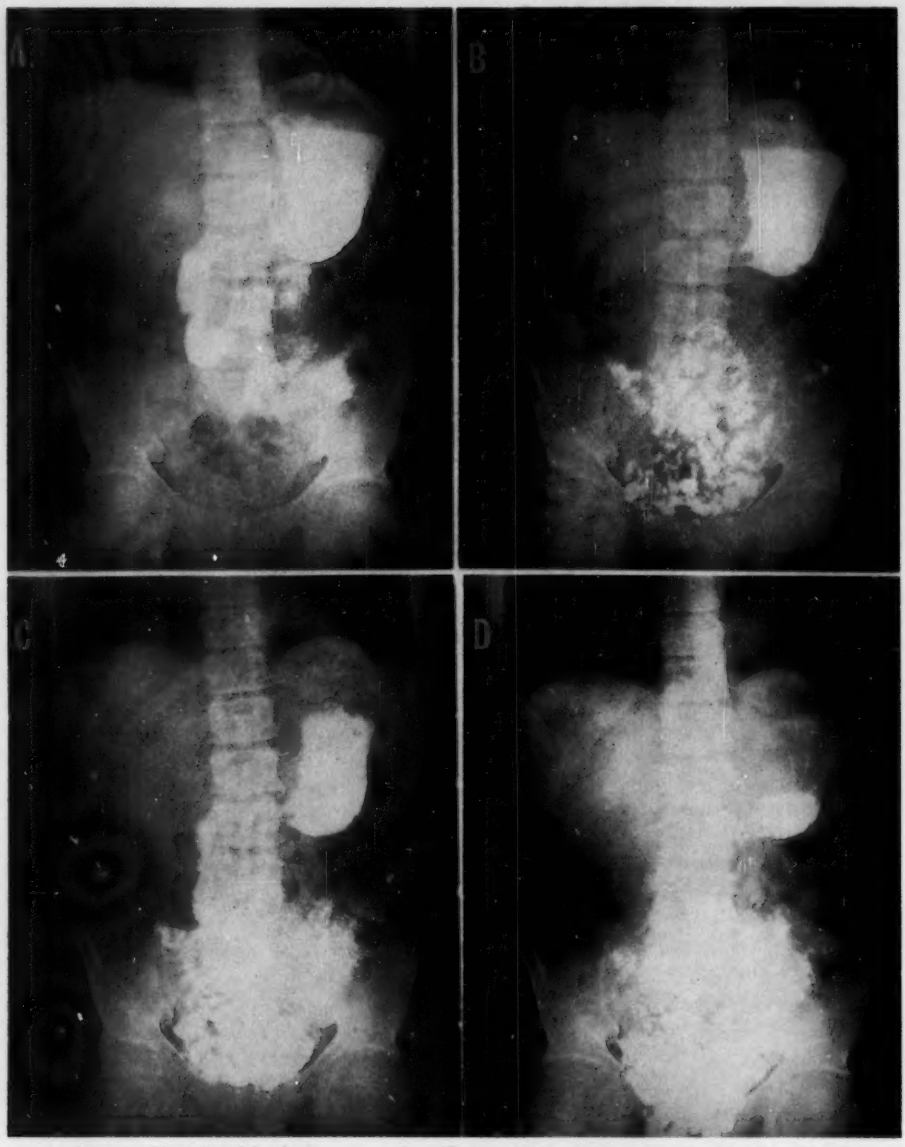

Fig. 4.—Upright abdominal x-rays of a 37-year-old man taken 1 (*A*), 20 (*B*), 45 (*C*) and 90 (*D*) minutes after ingestion of the barium food mixture. This patient had a hemigastrectomy vagotomy with a small stoma gastroduodenostomy.

Dietary Studies.—The undernourished patients who were severe dumpers and were maintained on a weigh-back diet usually did not eat enough to meet their daily caloric or nitrogen requirements. The symptomatic or asymptomatic dumpers who were given a constant analyzed diet did not have excessive losses of nitrogen and fat in their stools. The liquid stool passed by some of these patients after the ingestion of 50% glucose

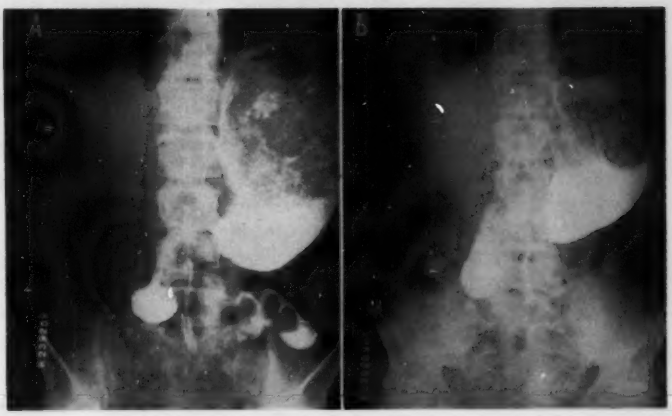

Fig. 5.—Upright abdominal x-rays of a 51-year-old man taken 1 minute after ingestion of the barium food mixture. They were obtained nine days (*A*) and seven months (*B*) after hemigastrectomy vagotomy with a small stoma gastroduodenostomy.

has been analyzed and found to contain up to 3 gm. of glucose per 100 ml. of stool. While fat and nitrogen was not measured in these stools, food particles were seen, and it is believed that the diarrheal stool associated with a high carbohydrate intake would contain excessive quantities of fat and nitrogen.

Challenge with Hyperosmolar Solution.—Symptoms were provoked by the ingestion of 50% glucose solution in all the patients who had a history of dumping symptoms associated with the taking of meals as well as some of the asymptomatic patients. All of these patients who developed symptoms after ingestion of 50% glucose solution also had rapid gastric emptying times demonstrated by their x-ray studies. The symptoms noted were those which are usually associated with dumping, namely, weakness, palpitation, sweating, flushing, nausea, abdominal discomfort, and in some instances the passage of a liquid stool. An occasional patient who had epigastric distress and vasomotor symptoms after the ingestion of 50% glucose was found to have these symptoms on the basis of distention of the stomach or afferent loop. These patients who were not relieved of their symptoms by lying down can be distinguished from the dumping patients by x-ray studies which show stasis in the gastric remnant or af-

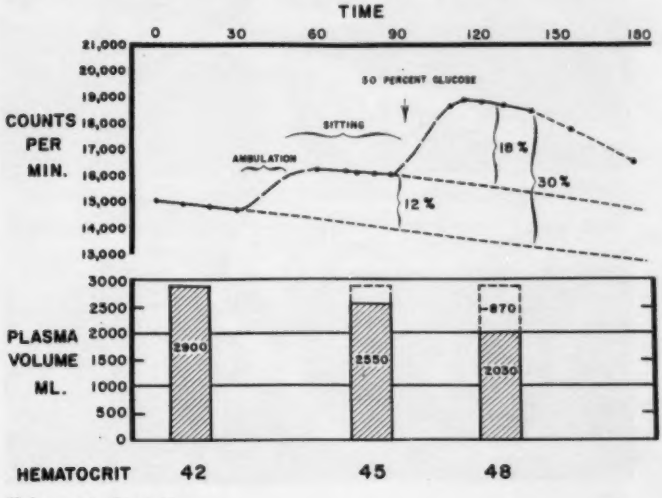

Fig. 6.—A schematic drawing showing the changes of plasma radioactivity, plasma volume, and hematocrit in symptomatic and in some latent symptomatic dumpers during and after ambulation and the ingestion of a hyperosmolar solution.

ferent loop due to partial obstruction. These patients showed marked improvement when the distended intestinal loop or stomach was decompressed by the insertion of a tube.

A decrease in plasma volume and an increase in peripheral blood flow was demonstrated when the dumpers had symptoms induced by the ingestion of 50% glucose. Figure 6 graphically shows the changes in plasma radioactivity, plasma volume, and hematocrit associated with a change from the recumbent position to ambulation as well as the changes which occurred after the ingestion of a 50% glucose solution. The maximum deviations from the expected control disappearance curve after ambulation and after ingestion of the hyperosmolar solution were used to determine the plasma volume changes. Thompson and his associates [21] demonstrated that a decrease of approximately 11% in plasma volume occurred in normal persons when they assumed the upright position. Subsequently Waterfield [23] demonstrated an average decrease of 15% under the same conditions. We believe that it is the added effect of the plasma volume decrease due to the ingestion of the 50% glucose superimposed on the decrease associated with ambulation which results in many of the vasomotor

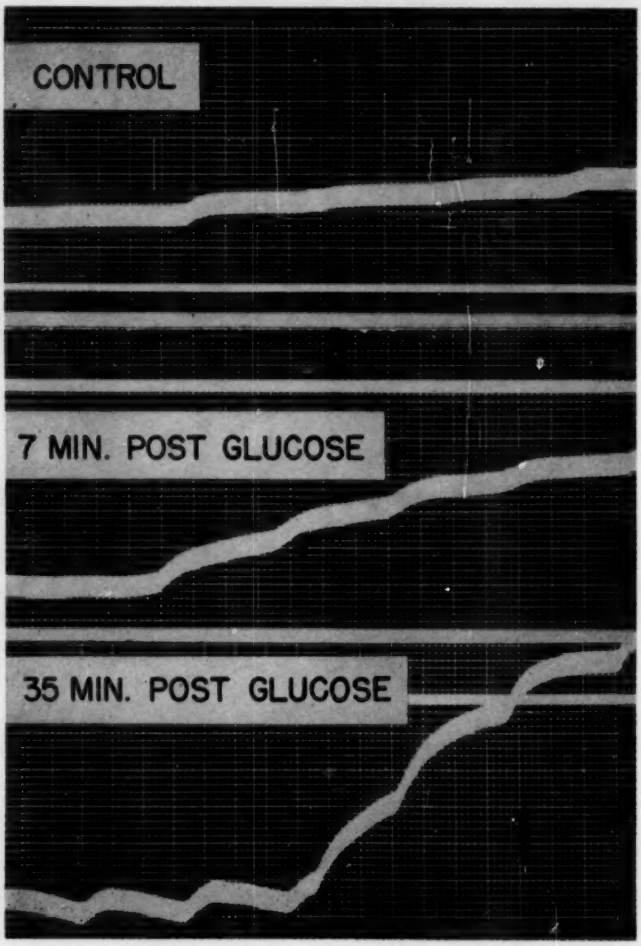

Fig. 7. — Plethysmographic records obtained from the study of a severe symptomatic dumper before and 7 and 45 minutes after the ingestion of 50% glucose solution. This patient's x-rays are shown in Figure 2.

symptoms noted in dumpers. This may also explain why many of them have their maximal reaction after breakfast. Plasma volume decreases of 5% to 20% after ambulation and 15% to 30% after ingestion of 50% glucose solution were noted in the symptomatic patients who were studied by this technique. When this test is employed, the plasma volume should be obtained after several hours of recumbency in a fasting patient prior to a 20 to 30-minute period of ambulation. After this the hyperosmolar solution should be ingested with the patient sitting up. Only in this way will an estimate be made of the changes in plasma volume which are comparable to those which occur when a patient eats breakfast. The determination of the plasma volume and its subsequent changes, especially under these circumstances, is not a reliable quantitative test. It does, however, provide an estimate of the direction and magnitude of the changes which occur and is of value in comparing the response of different patients to ambulation and the hypertonic glucose challenge.

Figure 7 shows plethysmographic records obtained on a patient before, and 7 and 35 minutes after she ingested 50% glucose. During the time the latter two records were obtained the patient was nauseated, weak, flushed, and sweating. The steeper slope of the 7- and 35-minute tracings, compared with that of the record taken before ingestion of the 50% glucose, is indicative of the increase in peripheral blood flow which occurred. Similar changes were noted in the plethysmographic records of other patients who had vasomotor symptoms after the ingestion of the hyperosmolar solution. These symptoms were severest in patients who had a decrease in plasma volume and peripheral vasodilation as demonstrated by increased peripheral blood flow.

Several of the patients who had rapid gastric emptying and small intestinal transit times did not develop symptoms after the ingestion of a 50% glucose solution. Symptoms might have been induced if more than 2 ml. of 50% glucose per kilogram of body weight had been given. These patients were usually stoical well-nourished persons who ate three normal meals a day without food idiosyncrasies and had no postcibal symptoms. They showed minimal plasma volume changes and no significant change in peripheral blood flow after ingestion of the hyperosmolar solution.

The patients who had hemigastrectomy, vagotomy with a small stoma gastroduodenostomy, or gastrojejunostomy did not have symptoms following the ingestion of the hypertonic glucose solution. These patients regained and maintained their expected normal weight.

Comment

We believe a more accurate determination of the incidence of the dumping syndrome can be obtained if evaluation of the patient includes interview, special x-ray studies as described above, measurement of daily caloric intake, and challenge with a hyperosmolar solution to provoke latent dumping symptoms. The last could be accomplished in some patients by observing symptoms which may occur during the x-ray study with the barium chocolate milk shake mixture.

These patients can be separated into the following categories according to the data obtained in the present study:

1. Asymptomatic, well-nourished patients with x-rays which showed gastric emptying and small intestinal transit times comparable to those seen in normal persons.

2. Asymptomatic, well-nourished patients with rapid gastric emptying with or without rapid small intestinal transit time.

3. Undernourished patients with or without symptoms (vasomotor and/or diarrhea) with rapid gastric emptying with or without rapid small intestinal transit time.

The patients who had a hemigastrectomy vagotomy with a small stoma (1 to 1.5 cm.) gastroduodenostomy or gastrojejunostomy were in the first group, while patients who had other types of operation with large stomal (greater than 2 cm.) anastomoses

were usually in Category 2 or 3. Some of the asymptomatic patients in Groups 2 and 3 could be classified as latent symptomatic dumpers since symptoms were provoked in them by the ingestion of a 50% glucose solution.

All of these patients who had a history of dumping symptoms, as well as those in whom we were able to provoke symptoms by the administration of a 50% glucose solution, exhibited an abnormally rapid gastric emptying time. We are in accord with the concept that the dumping syndrome is caused by the loss of the "reservoir" function of the stomach and the resultant rapid emptying of its contents into the upper jejunum. We also believe that while other mechanisms may be involved, the single most important factor governing the rate of gastric emptying is the size of the gastroduodenal or gastrojejunal stoma. Our experience indicates that any stoma which has an internal diameter of 2 cm. or more is a large stoma and is apt to result in abnormally rapid gastric emptying. We have also been impressed by the fact that there may not be a correlation between the surgeon's estimate of the stomal size and its function and that the only reliable way of determining stomal function (gastric emptying time) is by utilizing special roentgenographic studies comparable to the one described in this report.

We cannot completely explain from our data why some of the patients who showed rapid gastric emptying by x-ray were asyptomatic, well nourished, and did not develop symptoms when they ingested the 50% dextrose solution. The quantity, concentration, and rate of passage of sugar into the upper intestine as well as its rate of absorption and diffusion throughout the intestine may be an important factor in determining the amount of extracellular fluid shift and therefore the plasma volume deficit. It is probable that compensatory adjustments occur in these persons which prevent symptoms. Hinshaw and his associates demonstrated one possible mechanism. They showed that patients who had symptoms also exhibited increased peripheral blood flow by plethysmography, while asymptomatic patients had decreased peripheral blood flow or no change. We noted comparable changes in our studies. Compensatory factors such as cardiac output, epinephrine discharge, and other cardiovascular adjustments, etc., may well account for the lack of symptoms in such patients.

Conclusions

1. In order to obtain a true evaluation of the incidence of postgastrectomy abnormalities, it is necessary to combine a comprehensive interview with functional roentgenographic studies and a challenge with a hyperosmolar meal.

2. The term "dumping" should be used only to describe the rapid influx of ingested material into the small intestine (failure of stomach or stomach remnant to act as a reservoir).

3. The patients who had a small stoma (less than 2 cm.) gastroduodenostomy or gastrojejunostomy exhibited slow gastric emptying (maintenance of gastric reservoir).

4. While the gastric stasis which occurs with a small stoma anastomosis (less than 2 cm.) may slightly prolong the time until a normal diet may be taken, it has not been necessary to reoperate on any of these patients, and to date they have been free of all postgastrectomy abnormalities.

5. We feel that any anastomosis whether Hofmeister, Polya, Billroth I, etc., exceeding 2 cm. in internal diameter is too large and therefore permits dumping. Although most patients with dumping are well nourished and asymptomatic, we feel that the reservoir function of the stomach will be preserved by the use of a small stoma and that the signs and symptoms of dumping will be impossible.

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Adrenocortical Steroid Therapy Resulting in Unusual Gastrointestinal Complications

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The medical profession has become aware of complications that occur in patients suffering from disease of the gastrointestinal tract who receive adrenocortical steroid therapy. For instance, perforations occur in patients who have duodenal ulcer,[5,11,12,17] regional enteritis,[15,16] and ulcerative colitis.[4, 16,19] But physicians have been much less aware of complications that can occur in patients who give no previous history or present no symptoms or signs of gastrointestinal disease and who receive adrenocortical hormones.

It has been previously noted that the following complications may occur in patients with no previous gastrointestinal disease: production of peptic ulcer [5,8,12,14]; perforation of peptic ulcer of the stomach or duodenum [4,7,17]; bleeding from the stomach or duodenum from ulcer or gastritis [2,16]; development of ulcerative esophagitis [16]; development of acute pancreatitis or peripancreatic fat necrosis,[3] and perforation of the cecum.[10] There are some internists who do not believe that corticotropin (ACTH) or adrenocortical hormones are responsible for such complications.[9] It is interesting to note in this connection that peptic ulcer has been considered a rarity in patients with Addison's disease. Its infrequency appeared to be associated with a decreased secretion of hydrochloric acid. It has, however, been postulated by Thorne and associates that a low uropepsin secretion, which is invariably found in patients with Addison's disease, returns to normal or to elevated levels during replacement therapy. It was their feeling that an exaggerated gastric response to adrenal steroids occurred.[6] It has been reported by Traut [18] that, even in patients with achlorhydria, administration of these hormones can result in peptic ulcer, and he provides evidence to this effect. Recently Robert and Nezamis [13] showed that intensive cortisone therapy will produce stomach ulcers in rats. From the evidence, it does appear that adrenal steroids play a role in the production of peptic ulcers, but the exact process by which this occurs is still unknown. Neither is the mechanism of the production of other complications understood. It is evident that steroid therapy does create significant differences in both objective and subjective responses of patients, owing probably to its anti-inflammatory effects, so that catastrophic events can occur without recognition by the physician.[1]

The complications that have resulted in the past 10 years at the State University of Iowa Hospitals are tabulated in Table 1. These complications followed adrenocortical steroid therapy in patients who had no previous gastrointestinal disease either by history, physical examination, or laboratory examination. The patients received steroid therapy for a number of conditions. These are listed in Table 2. The patients who experienced massive upper gastrointestinal hemorrhage were handled satisfactorily, as

TABLE 1.—*Complications Resulting in Patients Who Had No Previous Gastrointestinal Disease*

Massive upper gastrointestinal hemorrhage	9
Perforation of the stomach	3
Perforation of the cecum	1
Perforation of the hepatic flexure of the colon	1
Production of acute duodenal ulcer	3

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TABLE 2.—*Conditions for Which Patients Received Steroid Therapy*

Rheumatoid arthritis
Asthma
Exfoliative dermatitis
Pemphigus
Irradiation proctitis
"Collagen" disease
Empiric

were those patients who had acute symptomatic duodenal ulcers. Two acute stomach perforations were also corrected without difficulty. But we erred on two types of complications. The first group included two patients with unexplained abdominal masses. The second group included generalized peritonitis from perforation of the cecum and from perforative appendicitis. In addition, a patient with a known peptic ulcer was operated upon for another condition and treated with corticotropin. He died from perforation of the ulcer. These three cases remained unrecognized, and death resulted. The purpose of the following case reports is to relate these cases and the lessons to be learned from them.

Report of Cases

CASE 1.—A 48-year-old white woman was admitted complaining of sharp knife-like epigastric pain, which had been present for three years but which had increased in severity during the previous two months, accompanied by loss of 16 lb. in weight. Because her physician had felt a mass in her epigastrium she was referred to the University Hospitals. The patient had suffered from rheumatoid arthritis for 15 years and had been receiving various types of corticoid therapy for the past six years. At the time of entrance she was taking 5 mg. of prednisone daily. A roentgenogram showed what was interpreted as a filling defect in the antrum of the stomach (Fig. 1). At operation a somewhat nodular mass was found involving the distal portion of the stomach, proximal duodenum, mesentery of the transverse colon, and right lobe of the liver. No liver metastases were present, and the pancreas did not appear unusual. Frozen sections at the time of surgery revealed only inflammatory tissue. The surgeon, feeling nevertheless this was a malignancy, carried out an en bloc resection of a portion of the right lobe of the liver, distal stomach, proximal duodenum, and a segment of the transverse colon. The stomach was anastomosed to the jejunum and an end-to-end anastomosis of the colon was done. The patient had an uneventful postoperative course. The pathologic study revealed two peptic ulcers of the stomach, with a perforation of one with abscess formation.

Figure 1

CASE 2.—A 68-year-old woman suffering from rheumatoid arthritis was admitted to the University Hospitals complaining of lower abdominal pain, headache, and nausea of one day's duration. The patient had been taking cortisone acetate for eight months for the arthritis, and at the time of admission was taking 7.5 mg. daily. She described the pain as a "stomach ache" of the lower abdomen. Physical examination was unrevealing. She was kept under observation for five days, and her symptoms abated and she was discharged. She returned six days later, complaining of constant nausea and a general abdominal soreness. Physical examination revealed a palpable golf-ball-sized mass in the upper right abdomen, which was slightly tender. It did not move on respiration. Roentgenograms of the upper and lower gastrointestinal tract were taken and interpreted as normal, and no diverticula were demonstrated (Fig. 2) in the colon. An exploratory laparotomy was carried out, and the mass was found adjacent to the stomach and pylorus and in the large bowel mesentery. It was removed and the pathologist reported this was inflammatory in nature. The permanent sections were interpreted as showing mesenteric hemorrhage, with granulation tissue and vascular thrombosis. The patient's postoperative course was complicated by nausea, vomiting, and fever, but she slowly improved and was discharged on her 15th postoperative day.

Figure 2

She returned 17 days later, complaining of abdominal pain, nausea, and vomiting. She had experienced no bowel movements in the previous five days; roetgenograms showed dilated small bowel and cecum, and a diagnosis of mechanical bowel obstruction was made. At operation the cecum was found to be markedly dilated, with an obstruction of the transverse colon at the site where the mass had been removed. A marked inflammatory reaction was present at this point. The colon was freed, and a cecostomy was performed. Repeated attempts at clamping the cecostomy tube resulted in abdominal distention, crampy pain, nausea, and vomiting. A barium enema displayed obstruction at the right hepatic flexure and no diverticula. She was reoperated upon approximately three weeks after the cecostomy was established, and a right hemicolectomy was carried out. Her postoperative course was smooth. The pathologic diagnosis was returned as a focal diverticulitis and chronic pericolitis with foreign-body reaction involving the right side of the transverse colon.

Comment.—These two cases point out the following: When a mass presents in the abdomen of a patient who has been on prolonged corticosteroid therapy one should suspect that a lesion which is inflammatory in character is present. In such a patient at the time of surgery, if the pathologist reports the biopsy as showing inflammatory tissue, the likelihood of perforative lesion with abscess formation is strong, and the surgical treatment should be adjusted accordingly.

CASE 3.—The patient first entered the Orthopedic Service of the University Hospitals at the age of 47 because of generalized acute rheumatic arthritis. He was seen again four years later, and the last admission was seven years later. On this occasion he complained of swelling and soreness of the knee and shoulder joints. In the two months prior to entrance the knee and elbow joints had been aspirated on several occasions, and a total of 325 mg. of hydrocortisone acetate had been injected. On this hospital admission a partial synoviectomy of the knee was performed. Ten hours after the operation the patient suddenly developed abdominal distention, nausea, and vomiting, accompanied by a fall in blood pressure. The abdomen was tympanitic and questionably tender. The pulse was 160/minute and the white blood count rose to 20,000 cu. mm. from a preoperative figure of 11,500. He was treated with a Levin tube and Wangensteen suction and was given parenteral fluids. Two days later a supine roentgenogram of the abdomen was taken, which showed dilated small and large bowel which was interpreted as intestinal ileus. On the eighth postoperative day, because of unrelenting symptoms, an upright roentgenogram was taken, which showed free air in the peritoneal cavity. An exploratory celiotomy was carried out, at which time a purulent exudate was found over the abdominal contents, most marked in the right lower quadrant. No perforation was found. Postoperatively, a stormy course ensued with the patient's body temperature rising daily to 103-104 F. He received penicillin and streptomycin. Later oxytetracycline was given, when bacteriologic studies showed that Escherichia coli and Pseudomonas aeruginosa organisms present were partially susceptible to this antibiotic agent. Five days later he received 25 mg. of hydrocortisone acetate intravenously along with 30 units of corticotropin. He died on the ninth postoperative day, and autopsy revealed the cause of death to be a generalized peritonitis secondary to a perforated cecum. He also had gastric and duodenal ulcers which were healing, as well as esophageal erosion.

CASE 4.—A 34-year-old white man was admitted to a hospital after an illness of five days. According to the home physician he complained of chills, fever, nausea, vomiting, and a dull pain in the midabdomen. Physical examination at that time revealed icterus, a tense abdomen, and rapid pulse. The white blood cell count was 14,800/cu. mm. The patient's temperature rose daily to 103-104 F, with episodes of shaking chills. Ag-

glutination tests for brucellosis and typhoid fever were reported as negative. He was treated with tetracycline, penicillin, and streptomycin without effect. Chloramphenicol was also used without success. Prednisone was given, and an abrupt drop in temperature to a normal level occurred; the jaundice cleared, and he had complete relief of symptoms. All antibiotics were then discontinued. Withdrawal of the prednisone resulted in a recrudescence of the fever and symptoms. Roentgenograms of the chest and abdomen were taken and interpreted as normal. A gallbladder dye was given, with faint visualization of the gallbladder, which did not appear unusual. Repeated blood cultures were sterile. The prednisone was repeated a second time as daily therapy, accompanied by tetracycline and sulfonamide, with relief of symptoms and return of body temperature to normal.

The patient was transferred to the Medical Service of the State University of Iowa Hospitals eight weeks after onset of the illness. On close questioning he stated the illness began suddenly one night with persistent pain in the right side of the abdomen and bloating. He became nauseated and vomited green, bitter liquid. Diarrhea appeared, followed then by the chills and fever. On the sixth day, jaundice developed and he had been hospitalized. At the time of entrance to the University Hospitals the patient was again icteric and was tender in the right upper quadrant of the abdomen. No masses or solid organs were palpable. A chest roentgenogram was interpreted as normal. The gallbladder did not visualize on roentgenography. Roentgenograms following a barium swallow showed a normal stomach that was dilated; the findings were interpreted as being suggestive of an obstruction in the duodenum. Supine roentgenogram of the abdomen the evening of the barium swallow showed gastric dilatation with barium still present in the fundus of the stomach. There was no evidence of intestinal ileus. The urine was negative to chemical and microscopical examination, and the hemoglobin level was 11 gm/100 ml. Various laboratory examinations were done, showing some disturbance of liver function tests. Two of five blood cultures grew Escherichia coli sensitive to chloramphenicol. This was given and, in addition, penicillin, streptomycin, and tetracycline were administered. During 10 days of hospitalization the temperature fluctuated between 94 and 106.8 F. Periods of coma alternated with episodes of delirium and confusion. He continued a downhill course, and died 10 days after entrance. The autopsy revealed pylephlebitis with multiple large hepatic abscesses secondary to an old appendiceal abscess. Thrombophlebitis of the appendiceal, gastroduodenal, portal, and hepatic veins was identified.

Comment.—The previous two cases point out the following: In any patient on adrenocortical steroid therapy who develops unusual signs or symptoms in the abdomen, the physician should be suspicious of perforation of a viscus. Roentgenograms either in the upright position or the lateral decubitus posture should be obtained to demonstrate whether free air is present or not. The signs and symptoms of a perforated viscus may be so modified by the antiphlogistic effects of adrenocortical steroid therapy as to mask a serious abdominal catastrophe. In any patient on corticosteroid therapy who develops suspicious symptoms or signs within the abdomen and the presence of free air is not demonstrated, the possibility, nevertheless, still exists that a perforation has occurred, and surgical exploration should be seriously considered. In all instances the dosage of hormones is not important. They may be large and produce no complications or they may be relatively small and produce the most critical of complications.

In patients with known disease of the stomach or bowel adrenocortical steroids must be used with caution. It is especially dangerous in the patient who is operated upon for some other lesion in which the anti-inflammatory effects are such as to mask the development of a catastrophe. For this reason the following case is included.

Case 5.—A 72-year-old white man had been diagnosed as having an adenocarcinoma of the prostate. At the time of his first admission he presented a history suggestive of duodenal ulcer, and this was confirmed by roentgenography. Six months later a transurethral resection was carried out, accompanied by the instillation of radioactive gold. He returned one month later, complaining of severe pain in the buttocks and thigh. Because of severe rectal pain sigmoidoscopy was done, which disclosed irradiation proctitis. A colostomy was advised and was carried out one month later. Seven days after operation, because of continued pain and tenesmus, he was started on corticotropin, 100 mg. daily. He went steadily downhill and died 16 days after the colostomy. Autopsy disclosed death was due to a perforating duodenal ulcer with generalized peritonitis. Another duodenal ulcer was present eroding into the pancreas.

Comment

Iatrogenic disease requiring surgical therapy will probably increase in the future because of the widespread use of adrenocortical steroid drugs. The dose is apparently not important, nor is the duration of therapy. Why certain patients develop complications and the mechanism of their production still remain a mystery. However, they are sufficiently frequent that all physicians should be aware that inherent in the utilization of such drugs lies the possibility of complications. In most instances, the therapy of these complications must, by necessity, be surgical in nature. In all patients receiving the drugs the development of any unusual symptom or sign should arouse the suspicion of the surgeon that a complication is developing.

Summary

Adrenocortical steroid therapy may result in perforation of a previously normal stomach or bowel. In any patient on adrenocortical therapy or who has been on such therapy in the past, a presenting abdominal mass may be the result of an old perforation of the bowel or stomach. If abdominal symptoms develop in a patient on adrenocortical steroid therapy, perforation of a viscus might be strongly considered, even if the symptoms and signs are bizarre.

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DISCUSSION

ON PAPERS BY DRS. BERRY AND SCHMIDT; BY DRS. KRIEGER, ABBOTT, BRADSHAW, AND LEVEY, AND BY DRS. SAUTTER AND ZIFFREN

DR. STANLEY HOERR, Cleveland: I should like to confine my remarks to the paper given by Dr. Krieger.

All of us who operate for ailments of the human stomach and duodenum have plenty of occasion to exercise our surgical conscience, Mr. President, because if we follow our patients we run into the occasional individual who, although cured of his ulcer, has a set of disabling symptoms which are worse than the ones for which we operated.

Perhaps the most constructive contribution of Drs. Krieger, Abbott, Bradshaw, and Levey has been their insistence on the orderly appraisal of these postgastrectomy woes. I think their systematic approach, with interview, special types of x-rays, and other special tests, is excellent in helping to differentiate the various causes, of which severe dumping is one.

The authors freely admit that they have not unraveled the mystery of why so many people who dump are free of symptoms, but of course the x-ray merely measures transit time and does not measure individual characteristics of mucous membranes or central nervous systems.

I personally have been slow to accept the thesis of the authors that a small stoma is important in preventing dumping. Perhaps I have been slow to accept it because I have very little confidence in my own ability to construct a stoma of exactly the right size. I am afraid I would make it so small that permanent retention would follow. If Dr. Krieger and Dr. Abbott have some technical hints as to how it should be done, I hope they will tell us.

On the other hand, it is difficult to argue with success. One of the patients in Dr. Abbott's series is a personal failure of my own, on whom I did a vagotomy and gastroenterostomy. The x-rays were shown here. We cured her of her duodenal ulcer, and we thought she was quite unreasonable in complaining about various other symptoms after the operation. Dr. Abbott and his group didn't think she was unreasonable and they cured her with a more radical approach than we had employed by taking out part of the stomach and giving her a small stoma.

I think this is an important contribution by these authors, and I am happy to have had this chance to discuss it.

DR. JAMES C. DRYE, Louisville: I arise to discuss the paper by Drs. Sautter and Ziffren.

There is no question but that these agents [adrenocortical steroids] do produce or precipitate lesions in the intestinal tract. From the paper today we have seen that they occur all up and down the tract. We became interested in this in the following manner:

[Slide] We were chiefly interested in the mechanism of how these things occur. We have had a number of patients who developed complications of preexisting ulcers. They either bled or perforated in the immediate postoperative period. We began to wonder about this, and we began to study gastric secretions in these patients and found that there was a marked rise in gastric secretion after either operation or accidental trauma. Then, of course, we wondered why this disease occurred. We studied the acids in these people and found there was a marked rise.

This slide shows a series of a few patients who developed these serious complications.

[Slide] These are some acid studies done after operations other than those on the stomach, showing gastric secretions afterwards.

[Slide] We thought from the work of Seymour Gray, who proposed that cortisone caused marked increase in gastric secretion, that this was due to cortisone. We went to the laboratory and tried to work it out on dogs, and we could not produce increased gastric secretion in dogs after trauma; so, we thought they acted differently from humans, and we tried cortisone on them. We were unable to produce an increased gastric secretion in the dogs with cortisone.

[Slide] Then we turned to man. This is just one of the slides of the many patients we studied. In ordinary doses we were unable to produce again an increase in gastric secretion, that is, free hydrochloric acid, in humans.

[Slide] We then studied pepsin, and again there was not much change.

Dr. Seymour Gray had reported that cortisone and these hormones produce increased gastric secretion. I talked to Dr. Gray. He was not using cortisone but was using corticotropin (ACTH). He said it was very difficult to produce it with cortisone, and he was using extremely large doses of corticotropin—far out of the realm of the ordinary therapeutic doses given.

The answer to the $64 question as to whether a patient who has been injured secretes hormones at that level, has not been answered. To me, it is unlikely he does. I think these perforations in the stomach and duodenum are similar to those in the lower intestinal tract, and are not due to

gastric hypersecretion, and we can only surmise that they may be due to a lack of healing power.

DR. HENRY SWANN, Denver: I greatly appreciate the privilege of the floor and the chance to discuss this interesting paper. I merely wish to report some experimental findings that have to bear on this presentation.

Stimulated by the work of Drs. Abbott, Zollinger, and others on the effect that stoma size apparently has on the dumping syndrome in patients, we designed an experiment whereby we could test the effect of stoma size on the objective changes that accompany the dumping syndrome. This was done by performing partial gastrectomy in eight dogs. In four of them a small stoma measuring 1 cm. in diameter was created, and in the other four a large stoma was made the entire breadth of the stomach. A test meal of hypertonic glucose was given to the animals, and the plasma volume and hematocrit changes were followed during the ensuing hours. After a mean of several runs was determined with the stomas in this fashion, the stoma sizes were reversed by changing the small stomas to large and vice versa at a second operation and the response to hypertonic glucose was repeated.

We anticipated that this experiment would show that there was less change in plasma volume as measured by RISA in the dogs with small stomas. Greatly to our surprise we found that the stoma size in no way was correlated with these changes.

Although this strikes a discordant note with the paper that has just been presented, perhaps a liquid test meal such as we employed flows through the essentially inert postgastrectomy stoma with a minimum of obstruction regardless of stoma size. We would like to suggest, however, that a clinical syndrome so obviously manifest by objective findings should, if possible, be quantitated in the experimental animal. Our efforts are merely one attempt to do this. Certainly stoma size will lend itself to such quantitation.

DR. HOWARD DORTON, Lexington, Ky.: This excellent report by Drs. Krieger, Abbott, Bradshaw, and Levey further confirms the thesis held by us and others that the direct hook-up of stomach to duodenum is probably the soundest from a body economy point of view. Our own work carried on continuously in Lexington since 1946 also would tend to bear this out.

Postoperative weight studies on approximately 300 of our duodenal ulcer patients subjected to vagotomy and simple pyloroplasty have been made periodically as our series has grown. There has been a consistent average weight gain of 18 lb. per patient.

Further analysis has shown that about 45% of the patients have done all of the gaining and that another 45% have remained steady at their preoperative weight level. The remaining 10% have lost weight, an average of 10 lb., usually by intent, since most of these were actually overweight at the time of surgery.

During this same interval we have treated a dozen or more marginal ulcer problems by vagotomy, disconnection of the gastrojejunostomy and reattachment of the small gastric remnant to the duodenum as a Billroth I procedure. In this small group the weight gain has been phenomenal and has ranged from 30 to 70 lb. per patient.

We do not propose that this weight gain represents a true fattening effect, but is merely a restoration of body weight to its projected normal level.

Our conclusion is this: We would like to suggest that body nutrition is not nearly so dependent upon the size of the gastric remnant as it is upon the maintenance of normal continuity of orderly digestive processes in an upper gastrointestinal tract free of disease.

DR. OWEN G. MCDONALD, Duluth, Minn.: I would like to commend Dr. Krieger and his associates for this careful follow-up study of postgastrectomized patients.

At the Duluth Clinic we are completing a study of all patients subjected to surgery for duodenal ulcer since 1942. We hope this will provide information about long-term as well as short-term results. With rare exceptions these patients have had a short loop posterior gastrojejunostomy after two-thirds to three-fourth resection and we have tried to establish a stomal opening of 2.5-3.0 cm.

Our survey has differed in two ways from that of the authors:

1. We have not done any in-patient studies of caloric consumption.

2. Our interviews have all been conducted by members of our department of internal medicine.

I believe there is a practical side to this problem which may be lost in all of our scientific studies. Our first interest should be in the patient and his interest is in such factors as (1) freedom from symptoms; (2) foods that he may or may not eat; (3) his ability to earn a living; (4) a reasonable weight, etc.

While one must not be stubborn about the surgical procedure employed, we think best results obtain when one performs a standardized procedure which he does well.

In an attempt to explain why some have rapid emptying or dumping after subtotal resection, I am impressed with the probability that most of these represent errors in selection of patients for operation. The patient with many psychosomatic complaints may succeed in misleading the surgeon about the severity of his pain, duration of treatment, etc., but all too often the true symptoms

and the patient's problems are not unfolded until after surgery.

One more question, which concerns evaluation of results: Consider the patient with a typical ulcer history of several years' duration, and one or more of the classical indications for surgery, but who, in addition has the accepted symptoms of spastic colitis or irritable bowel syndrome, whichever you prefer. He has a resection which relieves him of the symptoms for which surgery was performed, but he continues to have two, three, or four stools, usually in the morning, just as he did before surgery. Is he to be considered to have a poor result because of persistence of the rapid emptying he had before surgery?

Subtotal resection continues to produce good to excellent results in about 92% of our patients. We have had 3 deaths in over 300 consecutive resections for duodenal ulcer during the past 10 years. Two deaths occurred in patients operated upon under emergency conditions for uncontrolled hemorrhage, and one as a result of a pulmonary embolus.

We cannot claim the weight gain described by Dr. Dorton, nor do we feel competent enough to do pyloroplasties on some of the cases we reset.

Dr. Campbell Gardner, Montreal: I am interested in Dr. Berry's views. He challenged me yesterday to find something wrong with his paper. I wonder why he has chosen 2 cm. as an arbitary figure? He did not say 2 cm. in x-ray, or 2 cm. in the stomach itself as being the fatal dimension. If the ulcer is 1.99 cm. does that make a difference? Or, if it is 2.01 cm., does that make a difference? How does one measure it in the x-ray or in the stomach? I would like to know if a micrometer caliper is used.

As to whether to resect or not to resect immediately, I would be interested in knowing whether Dr. Berry himself, had he such an ulcer (2 cm.) would have it resected now in Montreal by some tiger-surgeon like me—or would he wait until he is back home?

Other than these musings, I have no feelings on the matter. If I had a gastric ulcer, I think I would have a little medical treatment for two or three weeks, and see if it healed up. If it did not, I would have it out. I believe I agree essentially with Dr. Berry.

As to the second paper—You know, I feel very hurt because the Central Surgical Association is considered to be a good and eminently fair Association, but I have discovered that of all the papers that were given about four years ago in Chicago, all were published except mine. I gave a paper on postgastrectomy syndromes. I presented the facts based on a five years' work and I thought they were truthful.

I proceeded to demonstrate how I could show a 93% good result or a 35% good result, depending upon how I juggled the figures around. [Laughter]

I was informed by the Editor of the Archives that the reason they did not publish the paper was because of the first sentence, which read: "Any doctor, before he publishes a paper, should go before a justice of the peace and swear to tell the truth, the whole truth, and nothing but the truth." [Laughter] The Editor thought this might harm the reputation of the medical profession.

Since then we have looked over about 2,000 cases done across Canada. We were in a peculiarly favorably position in doing it, because of the cooperation of the Department of Veterans Affairs. These cases had been done by every conceivable method one could think of. All sorts of tricks and turns had been used—postcolic and antecolic, iso- and antiperistaltic, vagotomies, and Billroths, and many others. What we found in the end was that, regardless of the operation used, the postgastrectomy syndromes occurred in about the same proportion.

We finally decided that we could predict those patients who were likely to have a postgastrectomy syndrome, regardless of whether they had a stomach this size or that size. Perhaps, after all, as we do not know the cause of duodenal ulcer, it is not strange that we cannot understand this complication of gastrectomy.

I would like to ask all of you this: Go back and see how many postgastrectomy syndromes occur in people who have had gastric ulcers. I would guess you will find that there are very few.

We sometimes have to operate because of bleeding or recurrent pain, or some other complication. We can save the patient from death in this way; but we have found, having followed our own cases very closely, that as long as the patient is subjected to the same sort of stress and strain as he had before, he or she will probably develop a postgastrectomy syndrome.

I would ask you all to think about the similarity of the postgastrectomy syndrome to the syndrome that develops in the first three months of pregnancy. There, you know, may lie a clue which is worth following.

Dr. Robert Watman, Columbus, Ohio: I agree with Dr. Gardner that this is a highly selective series. In our series at least, the ulcers from 2 to 5 cm. were the ones in which were found the largest percentage of malignancy.

Also, our radiologists are chary about calling a gastric ulcer benign. They know that this is a difficult diagnosis, and they are not perfectly willing to go out on a limb.

Even taking this favorable, highly selected series, I am impressed by some other statistics that appear in the "statistical jungle," namely, that 45% of

them failed on medical management, that there was a 14% recurrence rate in those that succeeded on medical management.

The incidence of carcinoma in this series is significant, but is lower than in most. It is usually reported as somewhere between 12% and 15%. We are impressed also by the fact that of the 15 cancers found in the early group, there were very favorable results, and in the 11 carcinomas operated upon later there were very poor results. It may be that this cancer is a "different disease," to be sure, but apparently time here is related significantly in some way.

So, to comment on this, first, the problem is generally a less selective one, as I am sure Dr. Berry has pointed out. Second, 19 of the 34 carcinomas in the total series were not found early by this regimen of management. Third, results were very good in those operated on early, and very poor in those operated on late.

One wonders if one of the pivotal points is what type of surgery is being offered to these patients. We turn from early surgery with a certain dread because of the mortality and morbidity that is implied. Perhaps we should think in terms of more frequent, fairly routine early surgery for gastric ulcer, but conservative surgery.

Perhaps it should be treated more like carcinoma of the breast. Prove the diagnosis of carcinoma by tissue examination. In those that prove benign relatively limited surgery gives good results and obviates much of the 45% or 55% poor medical result.

For those with a tissue diagnosis of malignancy, early and radical surgery may be performed.

Dr. William H. ReMine, Rochester, Minn.: I would like to confine my remarks to the paper by Drs. Sautter and Ziffren. I was very flattered to be asked to comment on it.

Drs. Sautter and Ziffren should be congratulated for bringing this problem to us and for stimulating a high degree of suspicion. We in surgery tend to overlook these possible complications while seeing patients on steroid therapy who do not have an obvious perforation or hemorrhage or history of previous difficulty.

In a report in 1953 from our institution there were 10 cases of serious gastrointestinal complication related to the administration of cortisone and corticotropin. Four of these had had no previous history or finding indicative of the ensuing difficulty.

After I was asked to discuss this paper I went over our records to find what information I could regarding this problem in patients receiving steroid therapy since the previous report. Of those patients receiving steroid therapy since then, who have developed complications, I was able to find 14 who had serious gastrointestinal complications without any previous history indicative of the problem. Five of these were duodenal ulcers and three were gastric ulcers. Most of these bled. There were two in the group of duodenal and gastric ulcers who had perforation. There were two small bowel ulcerations, two cecal ulcerations, and two rectosigmoidal ulcerations.

Of the entire group, two of the patients died as a result of perforation of the ulcerations, and these were the two that had ulceration of the cecal region.

The cause of these problems, I think, is quite intriguing. Spiro and his associates have reported the effect of administration of corticotropin on the excretion of uropepsin. They presented evidence that suggested that corticotropin stimulated the activity of the gastric glands by way of the adrenals, thus producing pepsin. Later the same group reported further on the effect of corticotropin on the stomach, and they found that the administration of 100 to 160 mg. of corticotropin daily to normal persons for three to four weeks produced approximately 200% increase in basal and nocturnal gastric secretions of acid and pepsin.

This, of course, does not explain what happens in the bowel below that point. Ulcerations and perforations of the bowel and segments which are not exposed to gastric secretions suggest that mechanisms other than hypersecretion of gastric juice is operating to produce these lesions. Whether these mechanisms are related to inhibition of inflammatory reactions or to the so-called antifibroplastic action which these hormones are thought to produce, is at present a matter of conjecture. It seems possible that factors which promote resistance to ulceration in the normal gastrointestinal tract may be suppressed in some manner by these hormones.

I think with the current-day usage of steroids and their vastly expanding use, particularly for rheumatoid arthritis patients, we may expect to see more and more of these bizarre problems. The steroids are being used indiscriminately, as we all know, by many physicians throughout the country, and I think the authors should be congratulated for bringing this to our attention.

Dr. Robert E. L. Berry, Ann Arbor, Mich.: To answer Dr. Gardner's questions: The 2 cm. ulcer was used because this is the type of ulcer-cancer that presents the most difficult problem of differential diagnosis. Entire reliance was placed upon the roentgenologist's evaluation of the size of the ulcer.

As to what would I do about my own gastric ulcer of the type described? I would want a four- to eight-day period of conservative treatment with reevaluation and decision for operation at that time. Although needless procrastination is unjusti-

fiable, at the same time there is little need for being panicked into an operation, as the issue for survival may well have been determined when the first cancer cell started multiplying and the biologic malignant potential of a given cancer thus established.

I would like to thank Drs. Gardner and Watman for their discussions.

DR. WILLIAM E. ABBOTT, Cleveland, Ohio: I would like to thank the discussants for their comments, but before answering their questions I would like to say that we believe that there are only a relatively few symptomatic dumpers and that most postgastrectomized persons are either asymptomatic or have learned how to get by with few or minimal symptoms, and therefore the majority of such patients maintain a fairly adequate state of nutrition. In other words, we believe that there are many patients who exhibit rapid gastric emptying and yet get along quite well and by interview would be classified as having a fair or good result.

We do want to stress the fact that we feel that the single most important examination that can be done is the taking of serial x-rays in the upright position following the ingestion of a barium food meal. This examination has not only been helpful in determining which patients have rapid gastric emptying, but we have also noted other abnormalities, such as distension of the afferent loop, biliary regurgitation due to a partial obstruction of the efferent loop, and occasionally marked stasis or obstruction to the outflow of material from the gastric remnant. Since the mixture we employ contains about 45 gm. of sugar it frequently provokes symptoms in patients who have learned to avoid them and thus provides the examiner with a more accurate evaluation of the operative technique employed.

In regard to Dr. Swann's comments, I would like to say that I heard their data presented by Drs. Eiseman and Brown at the College Meeting in Chicago last fall. In this report, they stated that the smallest stomal size which they used in their experiments was as large as the jejunum; hence it cannot be classified as a small stoma. Therefore, these workers studied animals with a large stoma and compared them with dogs with a larger stoma so their studies would not be comparable to ours and would be of little value in determining the importance of a small stoma versus a large stoma. In their study it would also have been important to have done serial x-rays after the ingestion of a barium food mixture so that the actual gastric emptying time could be determined. It should also be stressed that it is very difficult to evaluate studies done in the dogs, since this animal's stomach is normally in the horizontal position in contrast to the sitting or standing patient, whose stomach is in a vertical position. Since most of us sit when we eat, it is quite evident that a large stoma gastrojejunostomy would allow the recently ingested food to pass rapidly through the stomach remnant and enter the jejunum almost immediately. Several different investigators have shown that when a patient who has rapid gastric emptying in the upright position lies down and swallows food or barium, the ingested mixture stays in the stomach for a longer period of time even though a large stoma is present. Therefore, it is very important to stress the fact that all examinations and provocative tests in postgastrectomized patients should be done after a period of ambulation, with the patient in an upright or sitting position.

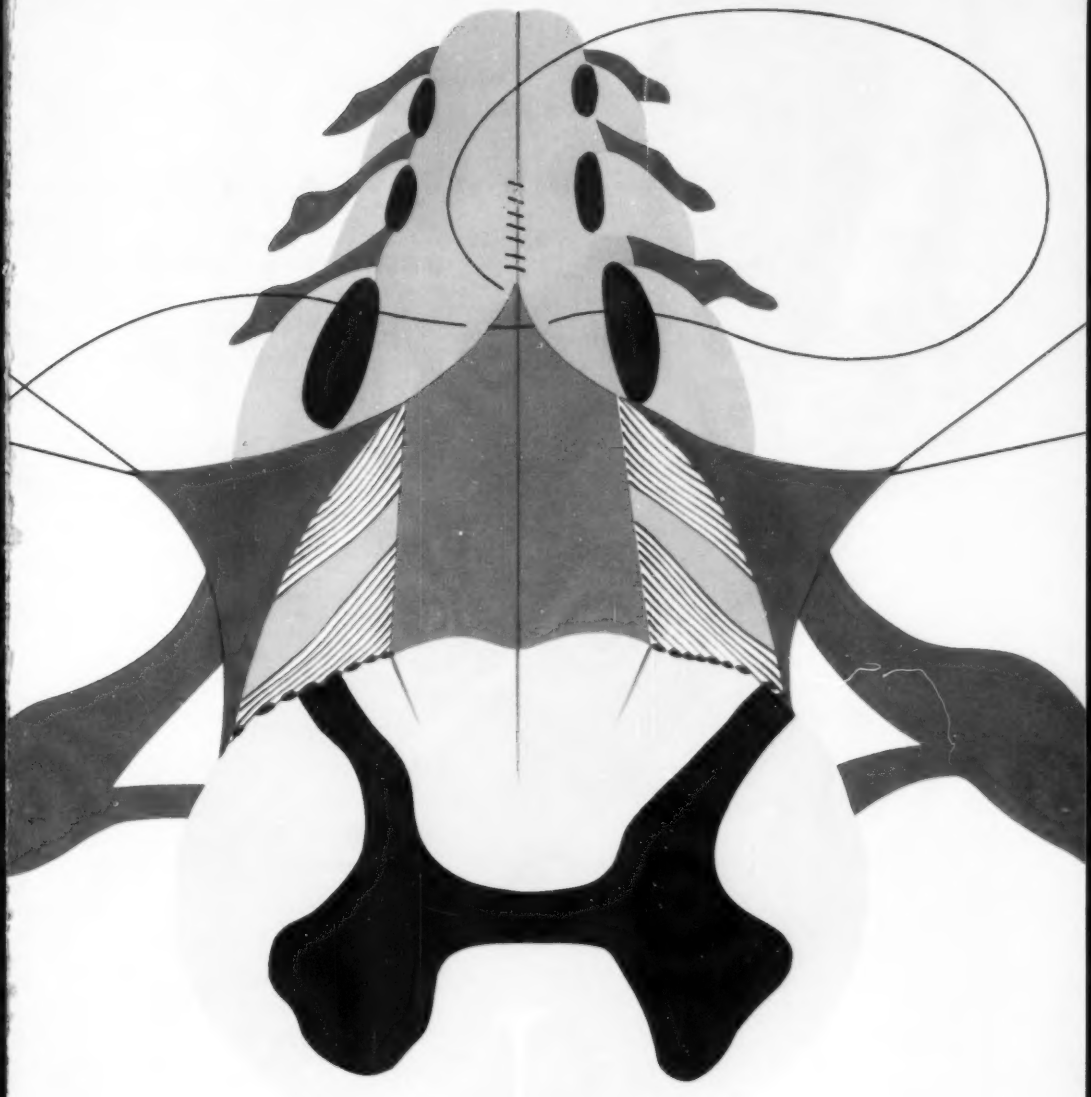
We want to think Dr. Hoerr for his kind remarks. He wondered if the very small stoma might not cause some difficulty. We have been more encouraged by the results as we have gained more experience. Originally we made some stomas which had an internal diameter of 2.5 to 3 cm., and in spite of our doing a gastroduodenal anastomosis, some of these patients, by x-rays demonstrated that we had not preserved the reservoir capacity of the stomach. Some of them have mild to moderate symptoms while others were asymptomatic. More recently we have made most of our stomas 1 to 2 cm. (internal diameter), and, although the patients often may not be able to eat as well during the first 5 to 25 days as those who have larger openings, the end-results have been very gratifying. These preliminary remarks may answer Dr. Dorton's question concerning the importance of the gastric remnant size. We are in complete agreement with him and many other workers that this has nothing to do with the problem. We and many other workers have noted extremely rapid gastric emptying and severe dumping symptoms in patients who have only had a gastrojejunostomy and thus had the entire stomach remaining. It should be remembered that from 1907 to 1934 Denéchau, Hertz, Mix, and Hartfall all independently described this syndrome after studying patients who had only a gastrojejunostomy.

We believe that the stomal size is more important than the type of anastomosis, since, as I mentioned previously, we have had patients who were converted to a Billroth I type of anastomosis and noted dumping if the stoma was large. We have also noted many patients who emptied their stomach at an essentially normal rate, after a small stoma gastrojejunostomy. I would like to call attention to the very excellent studies of Porter and Claman (*Ann. Surg.* 129:417, 1949), who studied 100 patients in whom they had done a small stoma gastrojejunostomy after a subtotal resection. In a comparable group of patients, operated on in

Edinburgh, a large stoma had been employed, and the instance of dumping, anemia, and undernutrition was frequently encountered in the latter group while it was rarely apparent in any of the patients who had a small stoma gastrojejunostomy. Therefore, we do not feel that the gastric remnant size or the reestablishment of continuity by way of the duodenum is the essential factor. It is quite apparent from our studies and from those of many other workers that the preservation of a gastric reservoir, which is best accomplished by making a small stoma, is the most important single factor in governing the end-result.

I am sorry that time will not permit a more detailed discussion of Dr. Garner's and Dr. McDonald's comments. In many instances we are in agreement with their statements but we would like to see them take serial x-rays of their patients after the ingestion of a barium food mixture. This would provide them with a more complete evaluation of their patients than can be obtained from an interview. It is difficult to believe that Dr. Gardner's observations could refute the study of several dozen workers here and abroad that are well documented by detailed studies published by outstanding medical journals throughout this continent as well as in England and Europe.

DR. SIDNEY E. ZIFFREN, Iowa City: We want to thank Drs. Drye and ReMine for their discussion. It is obvious these drugs can produce ulceration and perforation anywhere along the gastrointestinal tract, but the big mystery is why and how.



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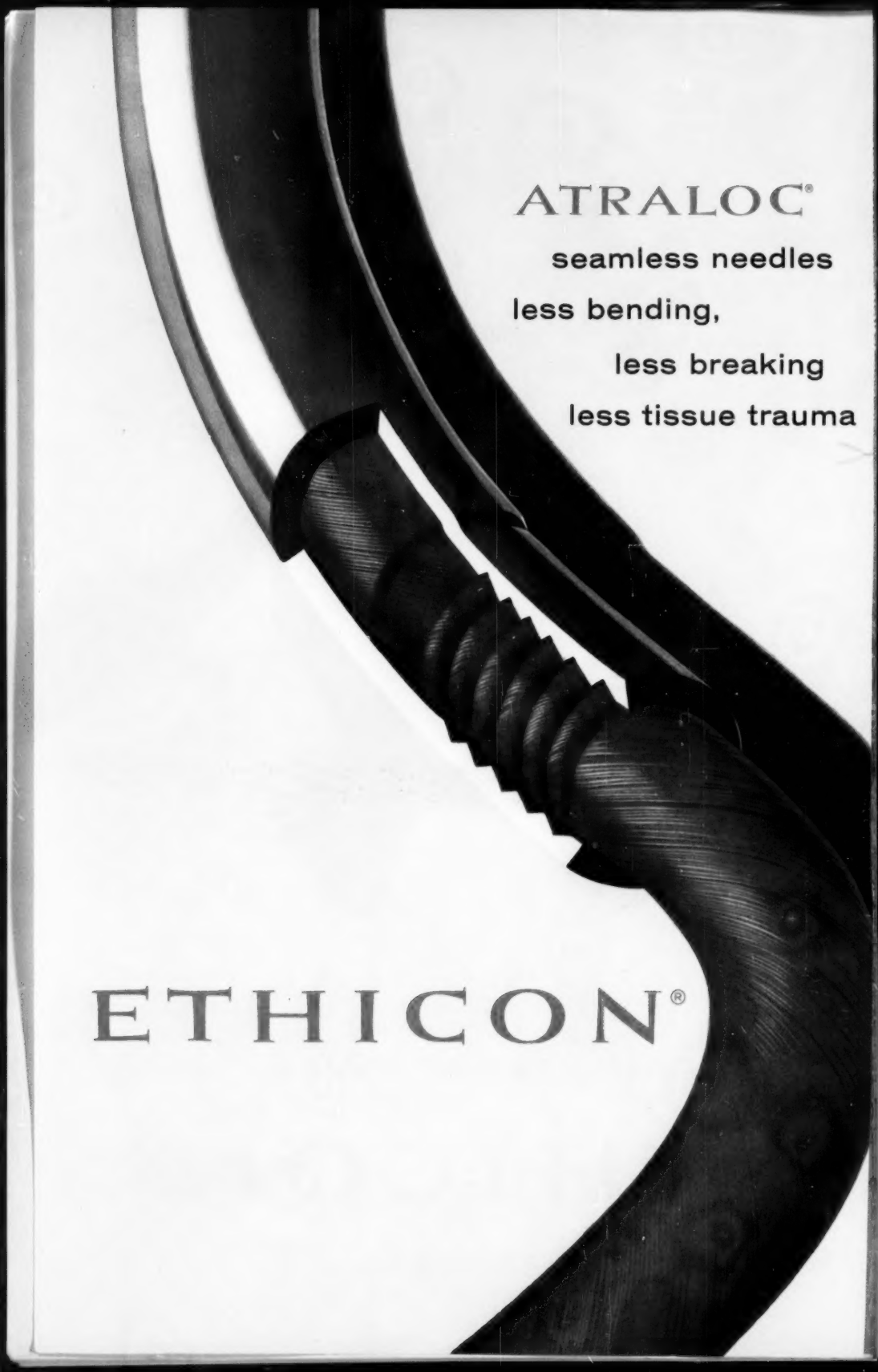
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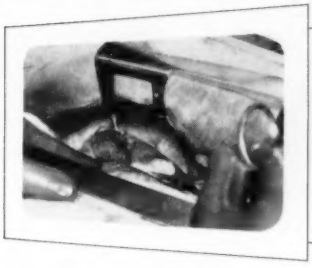

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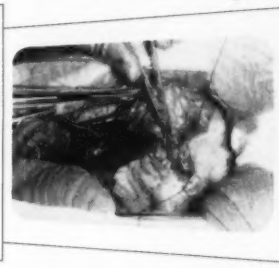

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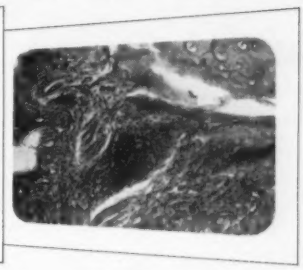

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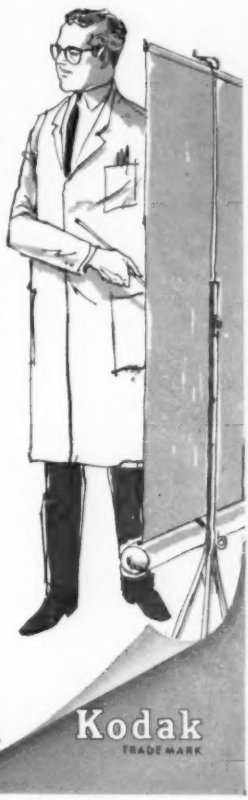

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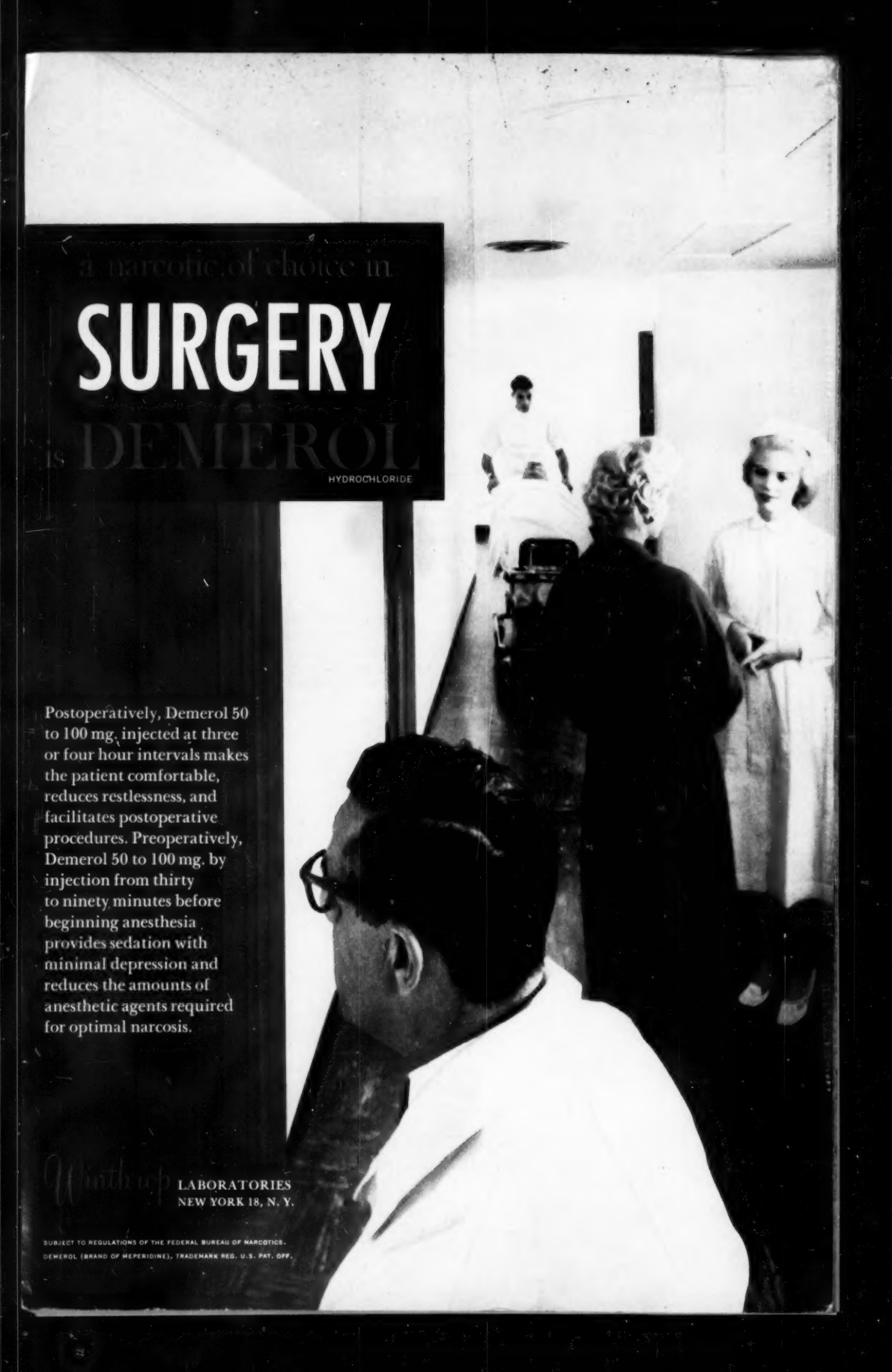
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